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THE PROTEOMORPHIC THEORY AND THE NEW MEDICINE

ABBREVIATED CHRONOLOGICAL LIST OF THE MORE IMPORTANT SCIENTIFIC AND HISTORICAL WRITINGS OF HENRY SMITH WILLIAMS

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THE PROTEOMORPHIC THEORY AND THE NEW MEDICINE

AN INTRODUCTION TO PROTEAL THERAPY

BY

HENRY SMITH WILLIAMS, B.Sc., M.D., LL.D.

Member of the National Committee for Mental Hygiene, and of the Hygiene Reference Board of the Life Extension Institute; successively Pathologist to the Iowa State Hospital at Independence; Assistant Physician to the Blackwell's Island and Bloomingdale Asylums, and Medical Superintendent of the New York Infant Asylum and the Randall's Island Hospitals, New York City.

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This Book

The Chart of a Blazed Trail in a Virgin Territory

Is Dedicated to

ORRILLA WEBSTER WILLIAMS,

Latter-day exemplar of the traditional spirit of the Roman matron and the Spartan mother, from whom in a large measure the present explorer acquired by inheritance and through childhood training the mental, moral, and physical equipment that made possible the conception and the successful prosecution of a pioneer journey not lacking in obstacles.

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FOREWORD

This book is essentially a Monograph detailing the author's personal discoveries, original theories, and practical experiences in a new domain of therapeutics.

It presents a series of new observations and certain novel theories of which it may unqualifiedly be affirmed that they are important if valid.

As a matter of course, not all these series of new observations and theories are on the same plane, either of importance, of originality, or of verisimilitude. It will be well, therefore, to give a preliminary outline of both theories and practical discoveries, with suggestions as to their relative importance in the estimate of the author. Such an outline will be of value to the reader, both in his preliminary appraisal of the matter presented and in orienting his detailed study of the evidence as given in the text.

First of all, as constituting the most general analysis, I would point out that three fundamental new discoveries are conceived to be represented. These are:

(1) A physiological discovery, to the effect that (a) the mononuclear leucocytes are the agents vitally concerned in beginning hydrolysis, and (b) the red corpuscles the agents concerned with the completion of decompounding of foreign proteins in the parenteral system. This is the essence of the Proteomorphic theory.

(2) The therapeutic discovery that foreign proteins and protein by-products introduced hypodermically into the parenteral system constitute antigens that stimulate responsive activities of the organism of such character as to aid tremendously in the fight of the organism against the evil effect of other foreign proteins of whatever character, introduced by pathological processes, including (a) the proteins associated with the bodies of pathogenic bacteria, (b) heterologous protein products associated with defective digestion and assimilation, and (c) autologous proteins associated with the hyperplasia of various organs, including the so-called malignant neoplasms. This conception, in itself an application of the Proteomorphic principle, furnishes the foundation for Non-specific Protein Therapy in general and Proteal Therapy in particular.

(3) The discovery that a single protein or combination of proteins used therapeutically cannot usually produce optimum results, because the system becomes sated or immunized and no

longer gives a maximum response. This principle, combined with the others, furnishes the basis for Proteal Therapy as at present developed.

The first of these discoveries was announced by the writer in *American Medicine* of October and November, 1914; the second had first detailed announcement in the writer's article in the *New York Medical Journal* of October 2, 1915. The two discoveries are interlinked and associated, but not necessarily interdependent. Either one of them might be proved fallacious without necessarily affecting the status of the other. But if both should be shown to be true, it will appear that corollaries of practical importance are associated with each that give mutual support to one another. The third discovery was first publicly announced in a *Monograph* issued December 1, 1916, under title of *The Proteal Treatment of Cancer and Allied Conditions.*

The above statement of principles may be considered as a fundamental analysis or summary of the most novel contents of this book. Let me now make an analysis of a slightly more detailed character, outlining the observed facts that appear to give support to one or the other of these principles, and the various collateral theories associated therewith.

The series of new facts, then, cited sequentially somewhat in the order of their discovery, comprise the following:

(1) Certain substances administered hypodermically have been observed to have a definite influence on the clinical progress of persons suffering from inoperable cancer of many types. These substances include extracts of plant products and animal products of many kinds; but they have this point in common—all of them contain protein or the products of partial protein hydrolysis.

(2) The observed modifications in cancer subjects through administration of these substances include: Alleviation of pain, modification of discharge, modification in the tumor itself, and modification in the general health and mental attitude of the patient.

(3) The same protein substances, administered hypodermically, have been observed to benefit markedly cases of (a) rheumatoid arthritis, (b) pulmonary tuberculosis, (c) pernicious anæmia, (d) intestinal toxæmia, (e) leukæmia, (f) Graves' disease, (g) psoriasis, (h) asthma, (i) arteriosclerosis, (j) neurasthenia, (k) primary and secondary anæmias.

(4) The clinical betterment of these cases has been observed to be associated with blood modifications of a definite and predictable character, namely: increase of hæmoglobin, increase in number of red corpuscles, increase of large mononuclear leucocytes, increase of eosinophiles, and modification of numbers of polunuclears and small lymphocytes in the direction of the nor-

mal; also with conspicuous qualitative changes in the direction of the normal.

(5) Physiological changes, including rises of temperature, quickened pulse, and a chill are not infrequently associated with the administration of the remedies in question, suggesting an anaphylactic reaction, not known to be produced by anything but protein or its products. This reaction appears not to be evoked in the same degree by partially hydrolyzed proteins.

(6) It has been observed that a condition of immunization appears to be attained sooner or later, after which the patient no longer responds in the same way to a particular protein; but that change to another protein may bring about a new response, with possibilities of cumulative beneficial effects.

The theories on which these observed facts are explained by the present writer are the following:

(1) The essential point of contact between the different substances administered hypodermically is their protein content (either the full molecule or products of partial hydrolysis).

(2) Any foreign protein injected into the parenteral system serves as an antigen and stimulates the defensive mechanism of the body to the production of antibodies capable of hydrolyzing foreign proteins of various types.

(3) Such antibodies are enzymic in character, and both specific and general in nature—that is to say, they hydrolyze the particular protein injected, but also other foreign proteins if present.

(4) The proteins of cancer are in a sense foreign proteins and fall within the scope of action of the enzymes called forth by the medical protein antigens. The degenerative diseases of middle life and old age are usually associated with disturbances of metabolism involving the parenteral invasion of foreign proteins or the undue retention or incomplete catabolism of protein end products. Tuberculosis falls within the same category because of associated secondary infections and the accumulation of localized foci of autologous and bacterial proteins subject to hydrolysis by the corpuscular enzymes.

(5) The mechanism particularly involved in the production of the protein-hydrolyzing enzymes is the blood-forming mechanism and its products, the white and red corpuscles.

(6) The general province of the white corpuscles is to deal with the full-sized protein molecule or its early cleavage products, and the province of the red corpuscles is to deal with the end products of polypeptid order, including bodies of the hypozanthin-zanthin-uric acid-urea series.

(7) The condition of the abnormal hyperplasia of the cells of various organs of the body, including the blood-forming organs, the coats of the arteries, and the cells of epithelial, endo-

thelial, and connective tissues, may be spoken of as a condition of hyperproteomorphism or the cancerous condition. All such conditions are more or less subject to clinical and physiological benefits from the administration of protein antigens—the effect being indirect, and conditioned on changes in corpuscular numbers or enzymic activities.

(8) Autolyzed cancer cells themselves serve as antigens, stimulating the blood-forming mechanism, but ultimately, in unfavorable cases, leading to the exhaustion and overpowering of this mechanism through over-stimulation and to the excessive destruction of corpuscles. Similar stimulation and possible exhaustion result from the parenteral presence of other foreign proteins, heterologous or autologous.

(9) Protein antigens as a whole may conveniently be spoken of as Proteantigens. Considering the observed action of these proteins in stimulating the increase of the ranks of large monocytes, the word Monocytosins may be used as a synonym for proteantigens. A more general and perhaps more appropriate word would be Cytogens. It is convenient to refer to the nonbacterial vegetable proteins, now for the first time used as therapeutic proteantigens or cytogens, under the name of Proteals. Animal substances such as white of egg and milk albumen, similarly used, may be spoken of as Proteils.

It goes without saying that the essential facts as to the action of the proteantigens are matters of chief importance. Theories are necessarily subordinate, and questions of terminology need give us no concern whatever. The latter are suggested here merely as matters of convenience.

There is a considerable body of evidence in support of all the observations and all the theories above cited; but naturally much more evidence for some than others. Beyond saying that the evidence is based on a first-hand study of a large number of cases, and on a fairly extensive series of microscopical observations, together with reports from a large group of associated physicians in various parts of the United States, I shall not attempt to summarize it here. The object of this book is to present the evidence somewhat in detail; yet even here the presentation is explicative rather than argumentative. I have not thought it expedient to cumber the text with long lists of repetitive cases, as I might readily have done. I have not duplicated the tabular records of my *Monograph* of 1916 (of which a new edition will appear presently). I have endeavored, rather, to summarize the salient facts and theories in the most condensed form consistent with clear exposition.

In view of the importance of the subject, I venture to hope that the candid reader will reserve judgment as to an estimate of

both facts and theories until he has attentively considered the evidence. It can scarcely be doubted, I think, that the principles of action of the white and red corpuscles and of bodily response to proteantigens are matters of fundamental importance, and I think also that the evidence in favor of the validity of these principles is of so cogent a character that it cannot be dismissed without a full and candid hearing.

When I first put forward the Proteomorphic Theory, I suggested that it opened up entirely new fields of cyto-therapy; and in the first exposition of the protein-antigen hypothesis, I suggested that the new method must stand on a par with serum therapy and vaccine therapy, if indeed it did not ultimately largely supplant these methods. Since these estimates were made, in October, 1914, and October, 1915, respectively, a great mass of new evidence has been collected, all seemingly in the same scale of the balance.

Confidence in the validity of the predictions just noted has grown with the accumulation of new evidence.

Possibly it may not be an exaggeration—should the above facts and theories be demonstrated to have validity—to speak of the protein response as constituting the most comprehensive therapeutic action known to modern medicine.

The Terminology of the New Science

In the *Monograph* of December 1, 1916, I cited the need of a new terminology for convenience in referring to the new therapeutics. I suggested the comprehensive term *Proteantigen* as a family name for all types of proteins used as antigens in therapeutics. As an alternate name, I suggested the word *Macrocytosin* (perhaps *Monocytosin* would be better), made appropriate by the observed increase of large monocytes that constitutes an important feature of the protein response.

I further introduced the word *Proteal* as a generic term for vegetable Proteantigens; on a par with the familiar words *Serum* (proteantigens derived from the blood of animals) and *Vaccine* (proteantigens of bacterial origin). A little later (April, 1917) in medical addresses I suggested the word *Proteil* as an additional member of the group, applied to proteantigens of animal origin other than serums—for example, protein extracts of animal organs, like the "autolysates" of Klinger and the "X-Substance" of Gwyer; preparations of milk protein, egg protein, and the like.

It was in the *Monograph* of December 1, 1916, also, that I first publicly enunciated the principle (backed at that time by a half-year of experimental observation) that it is necessary to change the type of proteantigen from time to time, in order to

get cumulative and optimum therapeutic effects—a principle of great theoretical interest in the light of the Proteomorphic Theory, and of fundamental importance in the practical administration of non-specific protein therapy.

In the succeeding pages the proteantigens chiefly referred to are Proteals of various types. These non-toxic vegetable proteins, as prepared in my private laboratory, are the agents with which the wide therapeutic possibilities of non-specific protein therapy and the essentials of the physiological response on which these possibilities are conditioned have been demonstrated in my hands and in the hands of associated physicians in various parts of the world. Full details as to the perfected methods of preparation of the Proteals hitherto used in my laboratory are given in the concluding chapter of the present book.

How the Proteals are Prepared

It is desirable to call attention here to the fact that two different types of protein extracts have been used, one containing the unbroken protein molecule, the other proteins partially hydrolyzed. The former were used almost exclusively until late in the year 1916. It will be well to recall that the results attained up to that time (and in particular the blood observations recorded) are ascribable to the unbroken protein molecule.

The essential procedure consists of the extraction of the protein from the ground seed or other vegetable substance with a salt solution; precipitation of the protein from this solution with hydrochloric or acetic acid; washing with distilled water; and the redissolving of the relatively pure protein with sodium hydroxide. The final solution is standardized by testing for nitrogen, so that as ultimately used it contains two per cent. protein, this percentage, however, being modified in various experimental tests. The solution, being kept slightly alkaline, can be sterilized by heat after sealing the ampules in which it is placed for safe and convenient subsequent handling.

The proteins thus preserved will, of course, be quite inert if given by the mouth. Administered hypodermically in doses of from ten to sixty minims the effects are striking and characteristic. They include a certain amount of local erythema at the point of injection; a feeling of giddiness; nausea, malaise, rise of temperature, and a more or less pronounced chill.

These familiar anaphylactic symptoms vary in their intensity with different patients, and are not produced in the same degree by different proteins. The protein of rape seed, for example, produces a much less severe general reaction than the protein of alfalfa seed.

After the above-described method of preparing the protein extracts had been employed for several months in my laboratory, a more expeditious method was devised, the essential features of which consist of boiling the powdered plant products for from two to four hours in a very dilute solution of hydrochloric acid (20 to 80 cubic centimeters of 10 per cent. hydrochloric acid to the liter of water, incorporating 50 to 100 grams of the plant powder); filtering; neutralizing with sodium hydroxide; refiltering; standardizing by the Kjeldahl nitrogen test; sealing in the ampules, and sterilizing for three days discontinuously.

This extract contains more extraneous matter (starch, glucose, lipoids, salts) than the other, but if properly prepared it is a perfectly transparent fluid, varying in color from amber to claret according to the specific protein content. The partially hydrolyzed protein (alkali albumen, proteose, peptone) does not coagulate on heating, but is partly precipitated by alcohol. Nitric acid precipitates it in part; the precipitate being dissolved on boiling, to reprecipitate on cooling (the familiar test for proteoses).

Proteals thus prepared are pleasant to administer, and as a rule produce little or no reaction, and, in ordinary dosage, no conspicuous systemic reaction. No case of anaphylactic shock from their use has been observed by me, or reported, although many thousand ampules of Proteals of this character have been sent from my laboratory to physicians in all parts of the western hemisphere, and administered to a large aggregate number of patients suffering from disturbances of protein metabolism associated with anæmias, intestinal toxæmias, neurasthenia, rheumatoid conditions, arteriosclerosis, cancer, psoriasis, asthma, and tuberculosis.

The Practical Administration of the Proteals

A few words about the practical administration of the Proteals above described will perhaps be of service to the physician who may consult this book without having time or inclination to read the more elaborate presentation of the subject which makes up the chief content of later chapters.

As above explained, Proteals are non-toxic vegetable proteins in sterile saline solution, standardized by a nitrogen test. They give opportunity for the application of non-specific protein therapy to a wide range of maladies associated with disturbed protein metabolism, with or without bacterial infection.

The name Proteal originated with me, and has not been applied, so far as I know, to any product made elsewhere than in my private laboratory. There is no restriction, however, on the use of the word or on the preparation of the products themselves. I hope presently to see the Proteals made in Board-of-Health

laboratories everywhere, as certain serums and vaccines are now made, for free distribution to the profession for treatment of the poor. Meantime, to the full extent of my personal resources, I shall see that no one is denied the benefactions of the Proteal treatment for want of money.

The Proteals hitherto used most extensively, as supplied from my laboratory to several hundred physicians in various parts of the world, are chiefly those made from Alfalfa seed, Alfalfa meal, Mustard seed, Rape seed, Hemp seed, and Millet seed. Numerous other vegetable materials and some animal materials have been tested experimentally, and some of these give promise of therapeutical usefulness as suppliers of proteins. Meantime, the available Proteals (which have passed entirely beyond the experimental stage, having been used for minimum periods of eighteen months, and administered to hundreds of patients in the aggregate) are sufficiently varied to meet a wide range of therapeutic needs.

The Proteals now available, as prepared in my laboratory, are distinguished merely by numbers—No. 29 contains the protein of Alfalfa meal; No. 36, Mustard seed protein; No. 38, Millet seed protein; No. 39, Alfalfa seed protein; No. 42, Rape seed protein. No. 37 is a mixture of the proteins of Mustard and Alfalfa; No. 40, a mixture of Mustard and Rape proteins; No. 45, a mixture of proteins of Alfalfa seed, Alfalfa meal, and Millet seed; No. 60, a mixture of proteins of Alfalfa seed and Alfalfa meal; No. 65, a mixture of the seed proteins of Alfalfa, Mustard, Millet, and Rape, and the protein of Alfalfa meal.

A newer series includes proteins of Oats, No. 50; Potato, No. 61; Wheat, No. 62; Carrot, No. 63; Flax, No. 64; Cotton, No. 66; Red Clover, No. 67; White Clover, No. 68; Spinach, No. 70.

A new combination, designated No. 75, includes the seed proteins of Red Clover, Cotton, Hemp, Flax, and Carrot. A mixture of this combination, in equal parts with the combination above designated as No. 65, gives ten types of protein and is designated Proteal No. 100.

All these Proteals are standardized on the basis of a two-per cent. protein solution, as above detailed; and the dosage and method of administration are substantially the same for all.

Administration of the Proteals is always hypodermic, preferably subcutaneous (not intramuscular or intravenous). The injection may advantageously be given into the back of the upper arm, about midway between elbow and shoulder. Some physicians prefer the gluteal region. If properly administered in suitable doses, the injection should cause very little local irritation, and practically no reaction, local or general. Patients differ considerably, however, in their sensitiveness.

The technique of administration is simple. It is well to sterilize the patient's skin by touching the point of injection with Tincture of Iodine and then with Alcohol. Touch the neck of the ampule with a file, and it may readily be broken. Insert a sterile hypodermic needle and withdraw the amount of the intended dose. A partially used ampule may be resealed by touching the neck immediately to a drop of melted sealing wax. If contaminated, the extract becomes an excellent culture medium and must, of course, be discarded.

The initial dose of any Proteal is from three to five minims. Repeat this daily or on alternate days until three or four doses have been given. Thereafter, if there has been no severe reaction, increase the dose by one or two minims with each administration until a satisfactory dosage is established for the particular case in hand.

The maximum dose varies with individual cases and with different maladies.

In anæmias, intestinal toxæmias, asthma, and tuberculosis, optimum results have been attained with a maximum dose of five to ten minims, administered on alternate days for a more or less protracted period. Obstinate cases of psoriasis have yielded to a similar dosage.

With rheumatic conditions, and especially rheumatoid arthritis, on the other hand, it is usually desirable to advance to a dosage of fifteen or twenty minims at least; sometimes to twenty-five or thirty minims, administered on alternate days or even daily.

Maximum doses and frequent administration are usually desirable, also, to get optimum and cumulative results, in cases of cancer, particularly where the neoplasm is large.

The blood count furnishes the best guide to dosage in administering the Proteals. The Proteal response is essentially a blood reaction. The ideal is to bring the hæmoglobin to approximately normal; the red corpuscle count to normal or supernormal; and the average leucocyte count to seven or eight thousand, with the differential count showing polynuclears relatively low, and large mononuclears advancing to high supernormal—ten, fifteen, or twenty per cent. of the total.

Where the blood count is not available, clinical symptoms must, of course, furnish a guide to dosage. It goes without saying that the administration of the Proteals gives opportunity for the exercise of skill and judgment on the part of the practitioner. The response and the needs of each individual patient should be carefully studied, as in the administration of any other line of scientific treatment.

A change of Proteals from time to time is essential in the treatment of most protracted cases, in order to secure cumulative

and optimum results. A measure of immunization to any particular type of protein appears to be developed in most cases, after periods varying from a few weeks to several months. A change of Proteals is then indicated. Each protein appears to produce an individual response, so the new Proteal should be given in minimum doses at first, advancing gradually to a maximum as with the first extract.

The possibility that a change of Proteals is indicated should always be considered when a patient, after a term of favorable progress, appears to reach a static period short of the desired optimum of improvement.

The wide range of therapeutic applicability of the Proteals is due to the fact that their response is a non-specific protein response, directly evoking modifications of the blood—as regards both its corpuscular elements and their enzymic activities—that are beneficial to the entire organism. This explains the observed anomaly that the same Proteal may be administered with benefit in conditions so widely removed, pathologically, as the anæmias, intestinal and other toxæmias, arteriosclerosis, rheumatoid conditions, asthma, tuberculosis, psoriasis, and cancer.

There are, indeed, few, if any, conditions involving disturbed protein metabolism in which the Proteals may not be appealed to with a large measure of confidence. The degree of improvement to be hoped for depends, of course, on the conditions of the individual case.

The particular Proteal to be selected for initial use in any individual case is to some extent a matter of experiment. I have pointed out that the Proteal response is largely non-specific. Observation shows that to a large extent the different Proteals are therapeutically interchangeable. Often it seems a matter of indifference as to which one is selected. Yet there are specific differences among the vegetable proteins, as a matter of course; and some of them evoke a much more active response than others.

I have suggested, as a general principle, that the proteins supplied by food products will, as a rule, evoke a less active response than the proteins of vegetables that have not been used as food by our race. Experience seems to justify this theory; for I have observed that proteins of the food cereals (also the proteins of milk and egg) and the proteins of mustard and rape seed are less active in therapeutic response than the proteins of millet seed and alfalfa.

In the treatment of individual cases, guided by this principle, I am likely to administer Mustard seed protein (Proteal No. 36) or Rape seed protein (Proteal No. 42) or their combination (Proteal No. 40) in the initial treatment of mild anæmias, with

the attendant conditions of "general debility," neurasthenia, etc., where a general tonic effect is desired. For treatment of severe rheumatoid conditions, of tuberculosis, and of cancer, I turn at once to a Proteal containing Alfalfa protein (Proteals No. 29, No. 39, or No. 60), or to the combination of proteins of Alfalfa seed, Alfalfa meal, and Millet, as represented by Proteal No. 45. Not infrequently I shift from one Proteal to another, experimentally, after a few doses; and sometimes I have found that an individual patient responds far better to one type of protein than to another, regardless of the type of malady.

In my office recently a case of tuberculosis, for example, showed slight modification of symptoms under Rape seed protein (No. 42), but responded promptly when a shift was made to Alfalfa protein (No. 60). Such individual idiosyncrasies are to be expected, in the light of our knowledge of varying susceptibility to the proteins of therapeutic serums, and should always be looked for when a case fails to respond to initial Proteal treatment. No conclusion should be drawn, however, until after the administration of at least eight or ten doses.

It should be borne in mind, also, that gradual and cumulative improvement, rather than sudden and spectacular changes, may be expected in the treatment of such chronic and intractable conditions as psoriasis and rheumatoid arthritis, even in the most favorable cases.

The Proteal response is totally different from the specific response of the therapeutic serums and vaccines. Proteals are not Serums or Vaccines. Each of these words is a generic term, having a restricted meaning, and the words cannot properly be used interchangeably. By definition, a Proteal is a solution of non-specific vegetable proteins. Serums are specific agents with an animal blood serum for the excipient. Vaccines, in the modern interpretation, are specific bacterial cultures containing the dead bodies of bacteria and their toxins.

Serums and vaccines necessarily contain proteins, and no doubt they have a non-specific action along with the desired specific action. To a limited extent they have been used non-specifically (typhoid vaccine, for example, in the treatment of arthritis), but such use seems to me unwarranted unless it shall appear that, when thus used, they have therapeutic advantages over the non-specific and non-toxic vegetable proteins (Proteals), which lack their toxicity.

The vaccines in particular, whatever their value in this connection, cannot be expected to duplicate the Proteal response, because their type of protein (bacterial) is different from that of the higher vegetables. As illustrating a typical difference in response, the vaccines invoke a polynucleosis, whereas a typical

feature of the Proteal response is a mononucleosis, and in particular a large monocytosis.

A pronounced anaphylactic reaction has not been observed in the use of the Proteals prepared by the newer method. The reason may be that the proteins in the Proteals as now prepared are partially hydrolyzed, appearing as proteoses, and perhaps in small part as peptones. The earlier Proteals, comprising saline and alcoholic extracts, contained the unbroken protein molecule, and their use in repeated and maximum dosage was attended with more or less marked anaphylactic reactions. Indeed, it was my custom to force the dosage until a marked systemic reaction was produced. The absence of this reaction makes the newer Proteals far pleasanter to administer, and far more acceptable to the patient, but leaves us without a clinical guide to maximum dosage in intractable cases.

It may fairly be said that no one at present knows what is the maximum permissible dose with any Proteal. Even with the old form of Proteal, containing the unbroken protein molecule, the dose was sometimes advanced (gradually) to forty, fifty, sixty, and even to ninety minims; and, although a severe systemic reaction was expected and even desired, no untoward result was ever observed. I have repeatedly given to guinea pigs day after day doses of proteins that, weight for weight, were equivalent to fifty or one hundred times the maximum dose administered therapeutically; and the animals thrive under the experiment.

Notwithstanding the relative non-toxicity of the Proteals, I regard it as desirable to administer the smallest doses that will produce results. If a dosage of six or eight minims will keep the blood conditions as I like to see them, with corresponding clinical improvement, I hold to such dosage. If it is necessary to go to a dosage of fifteen or twenty minims, there should be no hesitancy in doing so, but beyond this it is usually better to shorten the interval between administrations rather than to give inordinate single doses. These are matters, however, regarding which individual cases differ, as do also the preferences of different physicians. The experienced practitioner, guided by personal observations, will develop his own technique in the use of the Proteals as with other lines of treatment.

Development of the Proteal Method

The theory of action of Proteals and other non-specific proteins, which originated with the present writer (so far as I am aware, no other has been suggested), is based on my interpretation of the mechanism of immunization as first published

in *American Medicine* for October and November, 1914, under title of the Proteomorphic Theory. I made the first specific therapeutic application of the theory in detail to the treatment of a particular malady, with the explicit suggestion that the non-specific proteins would be applicable in combating all types of protein toxæmias, including bacterial diseases, in the *New York Medical Journal* of October 2, 1915. A more elaborate explication was given, with detailed study of the blood modifications attending the use of the Proteals, in a Monograph of 126 pages bearing the title *The Proteal Treatment of Cancer and Allied Conditions,* issued December 1, 1916. The name Proteal was first introduced (together with the name Proteantigen as a family name for all proteins used as antigens, including Serums and Vaccines as well as Proteals), and the principle that a single protein or combination of proteins must not be depended on to secure optimum results in the majority of cases was first publicly enunciated, in this Monograph, which bore the sub-title *A Practical Study of a New Therapeutic Principle as Interpreted in the Light of the Proteomorphic Theory.*

The practical results of Proteal therapy in my own hands and in the hands of several hundred associated physicians have been of a character calculated to arouse enthusiasm. I made a statistical analysis of 766 cases, treated by 152 physicians, in a preliminary report published in the *New York Medical Journal* of November 13, 1915. A considerable body of new evidence was available when my *Monograph* above cited was published a little over a year later, but this work was largely devoted to the theory of Proteal action, with especial reference to the modification of blood conditions, to which I had devoted assiduous attention, believing that to be the crux of the entire matter.

During the summer of 1917, in the course of a long lecture tour in the West, I delivered about one hundred addresses on Proteal Therapy before gatherings of medical men, including several County Medical Societies. The interest aroused is evidenced in the subsequent use of the Proteals by a large number of physicians who heard these addresses. The co-operation of these practitioners has been a valuable asset in further tending to establish the applications of the Proteals in a variety of maladies with which previous experience had been limited—including asthma and tuberculosis. The joint experience of this group of physicians and of others previously interested has served to fortify and extend my personal observations.

Other Non-specific Proteins

It should be clearly understood, however, that, whereas I make constant specific reference to the Proteals, and tell of the defi-

nite therapeutic advantages attained with their aid, there is no contention, explicit or implied, that the particular proteins thus used have any specific advantages over other types of proteins, of animal or vegetable origin, that may ultimately be introduced. New types of proteins, and new methods of extraction, are constantly being sought in my laboratory, and will presently be sought in numberless other laboratories, if I mistake not, as a result of the publication of the present book. It is easily within the possibilities that proteins far more desirable than any hitherto used may presently be made available. But that is a matter of mere detail. The thing of importance is that the *principle of protein response* has been—so I believe—conclusively demonstrated, and that simple extracts of the proteins of alfalfa seed, millet seed, rape seed, hemp seed, clover seed, cotton seed, and the like furnish the therapeutist with new and effective weapons in combating many prevalent maladies associated with disturbances of metabolism and the invasion of foreign proteins—maladies that, in the aggregate, take toll of hundreds of thousands of lives in the United States alone each year, and mar the health of uncounted millions.

Scientific Medicine Versus Empiricism

The physician who would handle these new therapeutic agents effectively must have a clear understanding of the principles that underlie their therapeutic action. To that end it is essential to gain a full knowledge of the important bearings of the Proteomorphic Theory. I would urge the professional reader who wishes to gain a really comprehensive grasp of the foundations of Non-specific Protein Therapy in general and of Proteal Therapy in particular to follow the chapters of this book sequentially, even though he should find some of them repellent because of their technicality.

When he has done so, it will be clear to him that Proteal Therapy differs from routine medical practice in that it may with propriety be said to be an applied science. Within the wide bounds of the application of the Non-specific Protein method, medicine ceases to be a merely empirical art. No man knows how or why morphine or strychnine or atropine or digitaline produce their perennially observed and perfectly recognized effects. With the Proteals, the case is different. We know how and why they operate. The physiological response that they evoke may be observed and demonstrated under the microscope. The dosage may be gauged in the same way. In administering them, we are no longer groping in the dark, along an empirical pathway. We are practising scientific medicine.

To be sure, our knowledge of this new science of Non-specific Protein Therapy is only in its rudiments. Prior to the appearance of my paper of October, 1914, the principles upon which it is based had not been explicitly formulated. Prior to October 2, 1915, no comprehensive statement of the therapeutic possibilities of the method had been published. Prior to July, 1916, no conclusive demonstration of the Protein principle, as such, had been made. And the first elaborate formulation of the microscopical evidence in support of the earlier inferences was published as recently as December 1, 1916. Meantime a collocation of the entire evidence available up to date, reproducing in full the original formulation of the Proteomorphic Theory itself, with sundry amplifications, and detailing the applications of the method throughout the wide domain of disturbed protein metabolism, is given for the first time in the present work, in combination with the second edition of the Monograph on *The Proteal Treatment of Cancer and Allied Conditions,* announced for issue early in April, 1918.

Notwithstanding the newness of the subject, however, Proteal therapy has passed far beyond the experimental stage. Much remains to be learned, of course, but much that is definite and tangible is already precisely known. I have personally administered many hundreds of doses of the various Proteals to patients suffering from a wide range of maladies, from simple asthenias and anæmias to pernicious anæmia, intestinal toxæmia, lymphatic leukæmia, arteriosclerosis, rheumatoid arthritis, goitre, cancer, and tuberculosis. My direct, personal office and bedside observation of patients under Proteal treatment comprises not far from five hundred cases. I have been professionally consulted by fellow-physicians and have advised with reference to the Proteal treatment of about two thousand additional cases. My office files contain more than six thousand letters dealing directly with the subject, received (and I may add, without exception, promptly answered) within the past two and a half years. My original blood-examination records number not far from twelve hundred.

Meantime more than fourteen thousand ampules of the various Proteals have been sent out from my private laboratory to cooperating members of the profession within the past year, and reports from these physicians give invaluable clues to the applications and limitations of the method.

The deductions from this substantial experience, including a full elaboration of my hematological discoveries, constituting the first comprehensive study of the Theory and Practice of Proteal Therapy, appear in the present book.

Here, and in the *Monograph* so frequently cited, I have attempted to justify by evidence my belief that the non-specific

protein response constitutes one of the most comprehensive principles known to scientific therapeutics, and that the Proteals furnish the practitioner with new weapons of genuine value in combating a long list of intractable maladies of middle life and old age, including anæmias, leukæmias, toxæmias, rheumatoid conditions, goitre, arteriosclerosis, asthma, tuberculosis, psoriasis, and cancer. The candid physician who has not had personal experience in the use of the Proteals may advantageously reserve judgment regarding the possibilities of the method until he has reviewed the evidence as presented in these books.

With a method so new there is necessarily much still to be tested. Some of the open problems will be discussed in the succeeding pages. But in the main the record here presented deals with the definite achievements already in hand. The work is by no means finished, but I repeat that it has passed far beyond the experimental stage. Proteal therapy is to-day a verity. In the hands of hundreds of practitioners it has proved its utility. When the newly discovered physiological laws on which it is based are generally known and recognized, the use of the method will become universal.

Such, at least, is the confident belief in which this book—the first attempt at comprehensive presentation of the Theory and Practice of Proteal Therapy in its wider relations—is offered to the medical profession.

THE PROTEOMORPHIC THEORY AND THE NEW MEDICINE

CHAPTER I

THE MECHANISM OF PROTEIN HYDROLYSIS AND IMMUNIZATION

The main theses of the Proteomorphic Theory are these: That the mechanism which gives the human organism partial or complete immunity against bacterial disease comprises what may be called the cytogenic or haematopoietic system—including lymphatics, bone marrow, and spleen—with its daughter cells the white and red blood corpuscles as its active agents, and with the liver as the excretory organ of the waste products incidental to the immunizing process; and that the same mechanism deals with all foreign proteins in the parenteral system; the case of the bacteria being only a special case within the general law of protein hydrolysis.

The white corpuscles are believed to begin hydrolysis of foreign protein, and the red corpuscles to complete the decompounding from the polypeptid stage, liberating amino-acids, and dealing also with residual end products of the zanthin-uric acid-urea series. Sundry antibodies of the general character of enzymes are coincidentally developed, their individual qualities being determined in response to the specific nature of the invading protein, bacterial or non-bacterial.

The theory assumes that the entire cellular system of the organism—viscera, muscles, brain—may be considered as a secondary apparatus, standing as it were in the background, ready to supplement the work of the chief immunizing agents. So general an implication as the latter may seem to savor of the nature of a truism; but it will appear that the theory ascribes a specific and definite part in the immunizing process to the body-cells in general and in particular, attempting to trace the precise rationale of their activity. Equally specific is the interpretation of the activities of the leucocytes and the red blood corpuscles, which are posited as the chief and controling mechanism in the process of protein hydrolysis in general and immunization in particular.

It will be well here at the outset to present a summary of the chief tenets of the theory, by way of orienting the mind of the

reader, and preparing him better to follow the detailed argument to which the ensuing hundred pages or so are devoted. The essentials of the theory, then, are the following:

1. The chief immunizing mechanism of the body is the cytogenic mechanism, of which the recognized members are the bone marrow, the spleen, and the lymphatic system. The active agents through which the process of immunization is carried out are the leucocytes and red blood corpuscles generated in the various organs of this system.

2. The prime function of the leucocyte, after it becomes a freely moving cell, is to facilitate and complete protein cleavage or digestion, preparing for assimilation (to the limit of its capacity) all foreign proteins that enter the blood stream. In pursuance of this function, it is provided with digestive enzymes, and with a mechanism for the production of special types of proteolytes to cleave an endless variety of protein molecules, and to counteract toxic proteins or enzymes due to bacterial activities.

It is believed that, generally speaking, the eosinophiles and large monocytes deal with the protein molecule unbroken or at an early stage of hydrolysis; the small lymphocytes and polynuclears with intermediate and later stages of hydrolysis; their functions, however, more or less overlapping, and their aggregate activities carrying the invading protein to the polypeptid stage of decompounding.

3. The red blood corpuscle completes the hydrolysis of polypeptid and allied protein products that find their way into the blood stream. It absorbs or counteracts the toxic residual molecules that are not completely hydrolyzed; and it antagonizes the products of bacterial activity, producing antitoxins. When ultimately autolyzed or destroyed, chiefly in the liver, it gives its protein and enzymes to the blood stream, and its waste products are discharged from the body through the bile duct and (in the form of uric acid, urea, and creatinine) through the kidneys. The functions of the red corpuscles in thus dealing with the end products of protein hydrolysis (reducing polypeptids to amino-acids and residual products) is conceived to be of fundamental importance, as indispensable as the function of carrying oxygen. An important specific feature includes the oxidizing of the purin bases to form uric acid, and the more or less complete transformation of the uric acid into urea.

4. The chief work of synthesizing protein out of amino-acids in the organism resides with the mother cells of the cytogenic apparatus—notably the bone marrow and the spleen. But the cells of each specialized tissue—muscles, brain, glands—can on occasion synthesize each its own special type of protein, utilizing the amino-acid building materials. Each tissue can also, on occa-

sion, hydrolyze nitrogenous molecules of the polypeptid order, and give out antitoxic ferments in response to specific toxins. But as a rule the tissues are shielded by the red blood corpuscles from the necessity of performing these functions.

5. The vast multitudes of red blood corpuscles, with an aggregate bulk of about four pounds in the ordinary human body, their substance having been synthesized by the mother cells out of amino-acids, constitute the chief source of the specific proteins in the blood stream, which proteins on being decompounded (possibly with the aid of the lymphocytes and polynuclears) are the prominent sources of bodily energy.

6. Every cell that can unite with a foreign proteid product can produce an "antibody" calculated to antagonize that product. The leucocytes and red blood corpuscles are the particular cells that come most in contact with such foreign bodies, and they are therefore the chief source of specific proteolytes and antibodies directed against the invaders. The presence in the blood stream of these specific proteolytes and antibodies, secreted by the leucocyte and red cells, and to a certain extent by the body-cells (backed up by the presence of an adequate army of leucocytes and red cells themselves, capable of producing more of the antibodies under stimulus of invasion), constitutes the condition of immunity.

7. Immunization to bacterial disease is merely a special case of protein assimilation. It has in the past been as necessary to acquire immunization against the dietetic proteins—oyster, fish, egg, fowl, milk, mutton, pork, beef—and against "benign" bacteria as against the most virulent bacteria.

8. So-called harmless or benign bacteria are those that have been long with us, and which, therefore, the leucocytic and erythrocytic mechanisms have learned adequately to combat and control. Virulent bacteria are the relatively rare ones or those that have visited us infrequently. A relatively benign bacterium may become malignant, however, through changed conditions leading it to ingest unwonted types of protein; or through developing exceptional vigor; or through invading the system in excessive numbers.

9. Protein anaphylaxis of any type (including "serum disease") is merely a special case of protein intoxication, strictly homologous with protein poisoning from the toxins of virulent bacteria. It results when a general proteolytic (leucocytic) enzyme is present in sufficient quantity to hydrolyze the foreign protein partly, while the red-cell mechanism is temporarily exhausted, so that cleavage cannot be completed, and the tissue cells—in particular the brain cells—are attacked. Protein anaphylaxis is strictly homologous with protein immunization. They are different as-

pects of the same subject corresponding respectively to the "passive phase" and the "active phase" of Wright's "opsonic index."

10. The activities of the cytogenic system, leading to an increase in the number of blood corpuscles and a stimulus to the activities of the individual corpuscles; and through these to completed protein assimilation and immunization, are governed in part by hormonic stimuli; the internal secretions actively engaged including those of the adreno-thyroid system and secretin from the duodenum.

11. The cytogenic system (including the bone marrow, the spleen, and the lymphatic glands) is a highly important member of the endocrinous system; the detached blood corpuscles are to be regarded as still a part of that system; and the study of the system as a whole offers a fruitful field for discovery of new methods in immunization and the treatment of infectious diseases.

The hypothesis of immunization thus summarized, being based on the activities of the cells, might appropriately enough be termed the Cytoclastic theory, were it not that the term seems too general and not sufficiently explicative. It might be termed the Corpuscular theory, in token of the rôle ascribed to both types of blood corpuscles, were it not that physical science has already usurped that term. To call it the Leucocytic theory would be quite inadequate, as it would credit only one member of the triumvirate, and would, moreover, signalize the least original portion of the theory itself. The term Erythrocytic theory would have somewhat greater propriety, as pointing out what is conceived to be the most important single agent in the immunizing process, and also as signalizing the most novel feature of the theory. But this term also is condemned by its obvious inadequacy.

On the whole, the term *Proteomorphic theory* is the most comprehensive and explicative one that suggests itself; inasmuch as the theory at all stages, and in its widest implications, has to do with the metamorphoses (mainly hydrolytic) of protein compounds.

It was through study of proteoclasis, mainly—in connection of course with the fairly wide survey of a good many allied fields—that the theory itself was elaborated. But for the data supplied by study of proteolytic activities, in connection with the metabolic processes of normal and abnormal digestion and assimilation, the theory could not have been conceived. So the word *proteomorphic* may be used to designate it with peculiar propriety.

It will appear in the course of the following exposition that a good many other laboratory and clinical observations, hitherto

utterly obscure or but vaguely interpreted, find clear and tangible explanation when viewed in the light of the proteomorphic theory.

It will be shown that the precise rôle of the leucocyte on one hand and the side-chain mechanism on the other are interpreted from a new point of view; that the red blood corpuscle is conceived to enter into the scheme of immunization as a masterful and dominating force, with all-important activities never hitherto ascribed to it; and that, as a whole, the scheme of immunization here presented has—if its tenets be accepted—a measure of comprehensiveness in the interpretation of the findings of physiologist, bacteriologist, and clinical pathologist that could not well be claimed for any theory of immunization heretofore submitted. More than that, the theory has pointed the way to a new field of therapeutics, already demonstrated to be large and important, the full limitations of which will not be determined for a long time to come—the field of Nonspecific Protein Therapy.

Before going on to the practical therapeutic developments of the idea, it is desirable to present the evidence for the Proteomorphic theory itself, drawn from various fields of biology and pathology.

In collating the evidence it will be necessary to summarize the results of experiments and observations gleaned from many different sources, some of which must necessarily be familiar to all medical readers, and all of which will perhaps be familiar to a few. This is unavoidable if the evidence in its totality is to be made generally comprehensible.

It will appear as we proceed that much of this evidence is indirect or circumstantial; yet in the aggregate, I believe, it establishes a strong presumption in favor of the validity of the theory advanced. And if the theory is accepted, certain very definite and rather important inferences as to practical therapeutic applications follow as matters of course. The study of the blood corpuscles assumes new interest and importance for the practical therapeutist. The genesis of anæmias of various types, including pernicious anæmia, is more clearly explained than ever before, on the assumption that the destruction of red corpuscles is due to excessive demands put upon them by the surcharging of the blood with protein end products. The differential count of the leucocytes other than the polynuclears becomes for the first time intelligible and susceptible of interpretation.

Specifically, it would appear that a monocytosis is as characteristic and as pathognomonic an evidence of protein intoxication as a polynucleosis is of bacterial infection; and that the artificial stimulation of a large monocytosis (as by hypodermic introduction of foreign proteins) is a therapeutic expedient sus-

ceptible of application in dealing with a wide range of maladies associated with disturbances of protein metabolism.

All this will be taken up in detail as we proceed. Our first concern, however, is with the previously established facts as to the systemic response to the invasions of proteins chiefly of the bacterial order.

Facts and Theories of Immunity

For generations physicians have been aware that an attack of a contagious disease tends to give the subject immunity against further attacks of that disease. The discovery of Jenner gave an inkling of the possibilities of preventing disease by inoculation, but this purely empirical procedure did not lead directly to any extension of the method. It was only after the bacteriologist had discovered the tangible cause of disease that a way was found to produce artificial immunization.

In 1887 Pasteur startled the world by demonstrating that a virulent bacillus could be attentuated as to its virulence by cultivation in an artificial medium, and that an animal inoculated with the virus thus produced was given immunity from the disease, even though subsequently inoculated with virulent germs. In 1890 Behring discovered that the blood of an animal thus immunized has power to transmit the immunizing principle, whatever it might be, to another animal if the blood serum of the immune animal is injected hypodermatically or intravenously. The diphtheria antitoxin thus developed by Behring, and a tetanus antitoxin discovered by Behring and Kitasato, were soon added to the armamentarium of the physician.

At about the same time, Ehrlich conducted his classical series of experiments with vegetable poisons, notably ricin and abrin (the toxic principles, respectively, of the castor-oil bean and the seed of jequirity). He found that an animal inoculated with either of these proteid substances developed an immunizing principle which, when mixed with the poison itself *in vitro* neutralized the poison. It was necessary to make the admixture in certain proportions, thus showing the chemical nature of the reaction. Ehrlich thought of the phenomenon in chemical terms; yet, for the purpose of bringing the matter vividly to the attention of the profession, he devised a mechanical scheme in explanation of the phenomenon of immunity which soon found almost universal acceptance, and which is often incorrectly thought of as suggesting something quite different from chemical combinations.

Ehrlich's tangible diagrams showing his "receptors" of the first, second, and third order; his haptophores and toxophores; his zymorphous and complementophile groups of the complex—all

depicted as tangible structures, some of them resembling hungry polywogs biting eagerly at inviting bits of protruding protoplasm of just the right size to make a mouthful—proved altogether alluring. A glance at such a diagram enables one to form a clear mental picture of the relations of receptive cells and complement and immune bodies in happy disregard of all possible chemical complexities.

In due course numerous workers proved the universality of application of the principles of the formation of the antibodies through the introduction of toxic agents into the organism. We learned of antitoxins, antiferments, cytotoxins, agglutinins, precipitins, and opsonins in the normal blood serum or developed specifically in response to the invasion of toxins; then it appeared that there may be anticytotoxins, antiferments, etc.; in bewildering profusion. And it was at least suggested that were our means of investigations sufficiently delicate we should find anti-antibodies in unending series, each new antidote becoming in turn a toxin and requiring an antidote; and the orgainc laboratory proving quite capable of developing series of such responsive mechanism *ad infinitum.*

To add to the confusion, different workers gave different names to the substances revealed in the course of their investigations; and in many cases they were talking of the same thing in terms of a different nomenclature. Thus the ferment that Ehrlich calls addiment was named by others alexine, by still others cytase and yet again complement—the last name being the one ultimately adopted by most authorities.

In the same way the immune bodies came to be known as amboceptor, copula, desmon, hilfskörper, zwischenkörper, fixateur substance, sensibilisatrice, etc. And it became a matter for dispute as to whether agglutinins, precipitins, and opsonins are identical one with another, and also as to the relations that these substances—recognized only by their effects—bear to the various hemolysins, bactericides, and bacteriolysins.

Out of the confusion, however, emerged pretty clearly the conception that there are two types of so-called bodies or chemicals involved in the immunizing process. One of these is a ferment-like substance which is thermolabile, its action being prevented by heating to a temperature of about sixty degrees centigrade; this substance being conveniently referred to as the complement. Joined with the complement in the immunizing process is a thermostable substance which may be comprehensively termed the immune body which apparently includes agglutinins, opsonins, and bacteriolysins (whether or not these are identical). The thermolabile complement is non-specific, in the sense that the same complement may unite with many types of

immune bodies. But the thermostable immune body is specific, in the sense that it is evoked in response to a specific protein or toxin (called an antigen), and is antidotal to the particular antigen that evokes it alone. A bacteriolysin, for example, evoked in response to the typhoid bacillus will not destroy the tetanus bacillus.

The validity of the conceptions associated with these terms is not to be questioned. Multitudes of experiments have shown that the terms "complement" and "immune body," and the ideas associated with them, are compatible with observable phenomena of the bacteriological world. The assumption that active complement must be present in order that immune body may be linked with the toxic agent to neutralize it, finds support in such practical work as Widal's agglutinizing test for typhoid fever and Wasserman's fixation-of-the-complement test for the diagnosis of syphilis. The conception that the toxic molecule has a "haptophore" group and a "toxophore" group and that the cell has receptors of a typical mechanical structure on which the haptophores adjust themselves is so tangible that it makes immediate and strange appeal to the imagination, or, better stated, it makes it unnecessary to call the imagination into play at all, the diagrams supplying its place.

I chanced to be living in London in 1900, and I had the pleasure of hearing Ehrlich deliver his Croonion Lecture before The Royal Society, expositing his epoch-making theory. Subsequently I visited Ehrlich at the famous Institute at Frankfort, and talked with him about newer aspects of the great problem of immunization, with particular reference to the possibilities of specific therapy, which were then holding his attention in connection with the development of salversan and the attempted selenium cancer specific. My own original investigations have led to developments rather along the line of extension of another field in which Ehrlich was a pioneer, namely the study of the tangible activities of the corpuscles; but like all workers in allied fields I have found aid and stimulation in the graphic designs with which Ehrlich attempted to make his conceptions intelligible.

Unquestionably these diagrams have proved very useful, and the entire mechanical conception has done much to promulgate widely a more or less comprehensible conception of the mechanism of immunity. But it is at least an open question as to whether these diagrams have not now served their purpose, and whether it may not be well to revert to a somewhat different point of view, and, ultimately, to adopt a terminology more in keeping with the expression of chemical ideas in general. For of course it would be absurd to imagine that the mechanical dia-

grams have any representation in the world of fact. They are figments of the imagination, and may serve some such useful purpose as picture blocks serve in teaching a child the alphabet. But as the time comes when the child puts aside the blocks and takes in hand the pen, so pathologists must ultimately lay aside the crude mechanism of haptophores and amboceptors and learn to deal with the phenomena of immunity in terms of the protein molecule and the chemical atom.

Protein Metabolism

To be sure the chemistry of the protein molecule is by no means as clearly understood as might be desired, even by specialists in biochemistry. But the researches of many workers in recent years have resulted in tearing the molecule apart in the laboratory, and in revealing the major part of its primary constituents. We are now gaining an inkling as to what really happens when proteid foods are taken into the digestive tracts and subjected to the digestive ferments. And we are beginning to realize that the subject has supreme importance from the standpoint of the student of infectious diseases, for the simple but all-sufficient reason that the microbic agents that cause these diseases are themselves protoplasmic bodies—that is to say, compounds of protein. I shall argue presently that the bacterial proteins are of a relatively unevolved type, comparable perhaps in complexity to peptones rather than to full-sized molecules of the proteins of higher plants and of animals; but in any event the difference is one of degree only. The bacterial substance, within its lipoid membrane, is a nitrogenous or proteid body.

When we reflect that there are always myriads of these proteid bodies in the digestive tract; and that legions of them on occasion find their way into the vascular system, and are there digested, the pertinence of the topic, in relation to protein metabolism, becomes evident.

And from the present standpoint the chief interest centers on the fact that there is in the human body one set of cells and one only that has been demonstrated to be able to digest and metamorphose the bacterial proteins when once they have invaded the blood stream—namely the leucocytes. What the ferments of the digestive tract accomplish in the case of the food proteins, is accomplished by ferments of the leucocyte in the case of the bacterial proteins with which it comes in contact.

I shall suggest that the function of the leucocyte in this capacity is far more general, having to do with the metamorphosis of many types of protein in addition to those that come with the bacteria; but for the moment it suffices to call attention to the

fact that the leucocyte is demonstrated to be able to deal with complex proteins, inasmuch as it is observed to engulf and assimilate protein-bearing bacteria *in toto*.

That the leucocyte actually performs this feat, was first demonstrated by Metchnikoff, and has been re-demonstrated thousands of times over in recent years, notably by the students of vaccine therapy. But the significance of this phenomenon, in its broader aspects, although at least partially conceived by Metchnikoff himself, was largely overlooked by his successors.

It must not be understood, however, that the capacities of the leucocyte as a proteoclastic agent have been altogether ignored by recent workers. On the contrary, it is probable that some of the physiological chemists have ascribed to the leucocyte in this connection a larger measure of activity than it actually exercises. Thus Hofmeister, stimulated no doubt by the discoveries of Metchnikoff, was led to ascribe to the leucocyte the all-important function of taking up the peptone believed (erroneously) to be absorbed through the intestinal wall, and converting it into protein either directly or with the aid of the adenoid tissues, thus making it available for assimilation by the body cells in general.

The peptone molecule, it will be recalled, is a cleavage product developed from the original protein molecule of a food protein hydrolyzed through the agency of the digestive ferments of stomach, upper intestine, and pancreas. The molecule of peptone has a molecular weight of only about four hundred, being therefore about one-fortieth the size of its parental protein molecule. To conceive that the leucocyte habitually takes this relatively small molecule as its building stone and elaborates the complex protein molecule the molecular weight of which runs high into the thousands—and does this in case of all the protein that the body utilizes—is to make an assumption that at the least seems amazing.

Yet Hofmeister thought that he found justification for this assumption in the fact that there is a marked postprandial leucocytosis. If the leucocyte does not perform the function of completing digestion of the food and facilitating assimilation, he argued, why should the number of leucocytes be habitually increased after a meal?

His reasoning seemed so valid that he has a good many followers. Cramer and Pringle, for example, and Noël Paton believe that the leucocyte plays a very important part in the assimilation of the protein food-products; and Pavy elaborated the hypothesis, arguing that the entire conversion of the food peptones into body protein is brought about by the leucocytes.

The particular type of leucocyte believed to be chiefly involved

is the lymphocyte, it having been shown by Paton, Goodal, and Gulland that the most marked postprandial increase in leucocytes occurs among the lymphocytes, although there is also increase among the polynuclears. My own researches, as will appear presently, show that the large monocyte is importantly involved, particularly when the parenteral protein to be dealt with includes the full-sized molecule, as frequently happens.

It is interesting to add that the leucocytic recruits come, according to Paton and Goodal, not from the intestinal lymphatic tissue, but from the marrow of the bones. Their development is stimulated, we must assume, either (1) directly by food products in the blood, or indirectly (2) through the agency of the sympathetic nervous system, or (3) in response to a hormone sent out from the intestine. It is conceivable that the hormone that produces this effect is the *secretin* of the duodenum, which is known to have a similar stimulating effect on the secretions of the pancreas.

Pavy developed the hypothesis, which Noël Paton has also advanced, that the leucocytes, after synthesizing the proteins, undergo autolysis, thus discharging their proteins into the blood, to furnish material for the tissue cells.

It seems probable that there is a measure of truth in the latter part of this hypothesis, referring to the autolysis of the leucocyte. In fact, the assumption that autolysis occurs seems unavoidable, in view of the observed rapid fluctuations in the leucocytic population even in health. But it is highly improbable that the leucocyte (in its mature state) synthesizes protein; or that the main function of handling protein-products of the intestine is dependent upon the leucocyte. As to this, Halliburton's suggestion, to the effect that the number of leucocytes in the blood stream is inadequate to perform this function in its entirety, seems fairly conclusive. Halliburton argues that the total blood stream contains only about one gram of lymphocytes; and even if this amount were doubled during digestion, "it is difficult to see how two grams of lymphocytes can tackle the enormous burden which every meal must put upon them." It should be observed, however, that the quantity of foreign protein in the blood at any one time is small. But the aggregate quantity of serum protein is, of course, relatively enormous, and in the last analysis it is clear that this is the product of the synthesis of food proteins.

According to the present view, the leucocytes are not called upon to "tackle" this problem, which is handled effectively by the mother cells that generate leucocytes and red corpuscles, notably the latter. These mother cells (in bone marrow, spleen, and in case of certain leucocytes lymphatics) synthesize protein

from its amino-acid elements in great quantity, as evidenced in the bodies of the corpuscles themselves. But the province of the mature corpuscles is to deal with proteins in a quite different way.

Their task is not that of synthesis but of proteolysis, and it is exercised, not only (1) in connection with the regular supply of food proteids, but (2) with bacterial proteins and (3) with exceptional increments of unbroken or only partially cleaved proteins that find their way by inadvertence into the vascular mechanism.

In view of the relatively small bulk of the cells making up the normal leucocyte population, it should be recalled that the amount of foreign protein in the blood serum at one time has been variously estimated between a minimum of .005 per cent. and a maximum of 0.12 to 0.19 per cent.—say from three to twelve grams in a person of average size.

In my original statement of the Proteomorphic theory, it was suggested that the polynuclear leucocyte deals with the unbroken proteins (bacterial or dietetic); the red corpuscle with partially cleaved molecules of the polypeptid order; and that the lymphocyte inaugurates the decompounding of the normal serum proteins, to supply energy for the activities of the digestive organs, the muscles, and the tissues in general. It now seems to me improbable, however, that the leucocytes are called upon to deal with the normal serum proteins. I shall revert to this aspect of the matter a little later.

I did not originally attempt a more detailed analysis of the relative share of the different types of white corpuscles in the work of proteolysis. My subsequent studies, however, which involved observation of the modified differential count in several hundred human subjects under influence of foreign proteins introduced parenterally, enabled me to elaborate the thesis, and to develop at least a provisional hypothesis as to the system of division of labor among the various groups of the leucocyte population.

These experimental observations and conclusions will be fully presented in later chapters of the present work. By way of anticipation, I may say here that they give the strongest possible support to the general thesis of the Proteomorphic theory as regards the essential proteolytic activities of the corpuscles. They also furnish suggestive clues to the solution of sundry problems as to the differential distribution of the various types of leucocytes, in health and disease, at different ages in the human subject, and among different orders of animals, that have hitherto gone quite unsolved.

In point of fact, very little is definitely known as to the pre-

cise mutual relations of the different types of leucocytes. There is a general impression that these fall into two groups, one of myelytic origin and the other of lymphatic origin. In the former group are the basophiles, the eosinophiles, the large mononuclears, and the neutrophiles. In the latter group are the lymphocytes. Whether or not the lymphocytes should be divided into small and large, as two different classes, is a matter regarding which the authorities are not agreed. Also the question of the precise origin and functions of the large monocytes is by no means settled. Ehrlich regarded them as the forms which, developing through a transitional stage, became transmuted to polynuclears. But it does not appear that there is any positive evidence in substantiation of this view.

Furthermore, it has been disputed as to whether the large lymphocytes are the parent forms of which the small lymphocytes are the daughter cells; or whether, on the other hand, the small lymphocyte grows and develops into a large lymphocyte.

Meantime, it does not appear that any one has given close study to the question as to the precise material out of which the bodies of the various leucocytes are developed, nor as to the specific distribution of their protein bodies after disintegration. It has been observed that there may be deviation of two thousand or three thousand leucocytes to the cubic millimeter under normal conditions in the course of a day. Reinart, for example, gives the average number of leucocytes at six o'clock in the morning as 5,125; and the average at 4 P.M. as 8,262. If we may accept such a variation as this as typical, it becomes obvious that the growth and disintegration of three thousand leucocytes to the cubic millimeter as a normal process during a period of twenty-four hours involves a cycle of protein metabolism that is highly significant. A very interesting question—and a question of great importance—arises as to whether the transmutation of raw materials, so to speak (with amino-acids for the ultimate building stones), through which the bodies of the leucocytes are built up takes place only in the mother organs of bone marrow and lymph nodes, or whether the free leucocytes in the blood stream continue to grow and develop, taking to themselves food pabulum, and passing through stages of individual development that may be properly spoken of as juvinility, maturity, and old age.

The well-known fact that the larger types of leucocytes exercise a phagocytic function, seeming to feed on the bodies of bacteria, gives strong support to the supposition that these cells are capable of ingesting protein pabulum and converting it into material for the increment of their own particular protein substance. It is believed by some observers that the granular structure of the leucocytes commonly spoken of as myelocytic (that

is to say, of bone-marrow origin) represents something comparable to a glandular substance, constituting a secreting mechanism. The secretions in question are supposed to be enzymic in character, representing the various antibodies, in particular the so-called complement.

According to one view, the granular leucocytes are all of bone-marrow origin, and constitute a class apart. But this view is obviously inconsistent with Ehrlich's claim that the large non-granular mononuclear leucocytes develop individually into neutrophiles.

Evidence in the matter is by no means as conclusive as could be desired, yet it is universally admitted that different organs of the body may on occasion take on the function of leucocyte-production; and it may very well be questioned whether there is any such distinct and fundamental difference between the blood-forming cells of the bone marrow and the similar cells of the lymphatic system as has sometimes been suggested. It may fairly be assumed, however, on embryological grounds that the lymphatic system constitutes a somewhat more primordial structure than the bone marrow, inasmuch as the latter is a relatively late development in the fœtus. But, on the other hand, many observers are disposed to trace the origin of the primitive forms of cells that appear in the blood under certain abnormal conditions (notably the leukæmias) to the bone marrow rather than to the lymphatic system.

It is more than likely that, when the systemic disturbance is sufficiently profound, both sets of organs may revert to a somewhat primordial manner of functioning, and put out cells of a more embryonic type than the ones usually sent into circulation.

By way of anticipation, I may say that in a later chapter of this book I shall suggest an hypothesis of the specific functions of the different types of leucocytes according to which the eosinophiles deal with the unbroken protein molecule, the large monocytes with full protein molecules and proteoses, the small lymphocytes with proteoses and peptones, the polynuclears with peptones and polypeptids, and the red corpuscles with polypeptids and amino-acids. It is further suggested that the polynuclears have to do with the digestion of lipoids and fats.

Details as these elaborations of the Proteomorphic theory can more appropriately be given after the general preliminary statement of them, to which the present chapter is chiefly devoted, has been made. Meantime, however, I venture again to depart from chronological sequence to the extent of citing two series of laboratory investigation by independent workers that have been carried out since the original publication of the Proteomorphic theory, and which in themselves furnish strong presumptive

evidence of the validity of (1) the general thesis that the corpuscles deal with foreign proteins, and (2) the important feature of the theory which ascribes to the red corpuscles the work of ultimate proteolysis and oxidation of the split molecules of the order of polypeptids.

The experiments that (if I correctly interpret them) throw corroborative light on the first-mentioned aspect of the Proteomorphic theory were made by Drs. M. W. Manwaring and Yoshio Kusama, of the Department of Bacteriology and Immunity of Leland Stanford, Jr., University, as recorded in the *Proceedings* of the Society for Experimental Biology and Medicine, of May 24, 1916. These experiments go to show that the blood corpuscles of a rabbit actively absorb goat serum proteins, whether the goat serum is mixed with the (defibrinated) rabbit's blood in a receptacle outside the body or whether it is injected into the system of the living rabbit.

This observation, obviously, gives the strongest support to the assumption of the Proteomorphic theory that the blood corpuscles are the agents chiefly concerned in dealing with foreign proteins; the assumption that forms the chief basis for the explanation of the therapeutic action of the proteal remedies with which the present monograph is concerned.

It should be added that, in the experiments just cited, it is further recorded that about 25 per cent. of the goat protein may remain in the rabbit's blood serum. "If the serum and corpuscle fractions (of the blood), are allowed to undergo independent autolysis (10 hrs., 37° C.) a distinct restoration of the goat protein is observed in each fraction. The restoration of the protein in the corpuscle fraction, however, is usually much more pronounced than that in the serum fraction, and may amount to as much as 50 per cent. of the total protein originally added to the blood."

From this it would appear that something like 25 per cent. of the goat serum originally injected is unrecovered, presumably having been hydrolyzed to a stage of decomposition at which it is no longer recognized as goat protein.

It would appear to be a logical inference that such hydrolysis of the goat serum proteins has been effected by enzymes generated in the bodies of the corpuscles which, according to the observations of the experimenters, constituted the chief medium for absorption of the foreign proteins. As far as they go, these experiments afford direct collaboration of one of the principal theses of the proteomorphic theory.

Possibly it may seem surprising that so large a proportion of the goat serum proteins remained unhydrolyzed after 10 hours' maceration. It must be obvious, however, that corpuscles under-

going autolysis outside the body may have far less enzymic activity than they would exhibit under normal conditions. But in addition to this it should be observed that the amount of goat serum introduced in these experiments was enormously large as contrasted with any doses of foreign protein administered therapeutically to the human subject, amounting, in fact, to one per cent. of the rabbit's blood. Assuming that the goat serum comprises at least 20 per cent. of proteins, the amount of foreign protein thus introduced would constitute one-fifth of one per cent. of the total bulk of the rabbit's blood.

That the corpuscles of the rabbit's blood were able to absorb at least 50 per cent. of this shows remarkable capacity on the part of the corpuscles for handling foreign proteins that invade the medium in which they lie.

As a still further anticipation of matter to be discussed in detail later, it may be noted that the normal proteals under consideration in this book contain only 3 mgm. of nitrogen to the cubic centimeter, or the equivalent of less than 2 per cent. of vegetable proteins. Meantime the amount of this 2 per cent. solution of proteins used in a hypodermic dose is only one or two cubic centimeters, as a rule; and almost never more than 3 or 4 cubic centimeters. Such a dose, introduced into the large quantity of blood in the human body, obviously constitutes an infinitesimal protein intrusion in comparison with the one per cent. of goat serum mixed with the rabbit blood in the experiments of Manwaring and Kusama.

Since these experiments now give us an inkling of the capacity of the blood corpuscle, the thought not unnaturally suggests itself that possibly we have hitherto used proteals in much smaller doses than might be permissible or advantageous. Here, obviously, is an interesting field for future experimentation, in connection with cases that have proved intractable to the proteal medication as hitherto administered. It must be recalled, however, that it has been customary to carry the dosage to the point of producing an anaphylactic response, and that with most patients this is likely to occur with a dose of thirty minims or less of a two per cent. protein solution. On the other hand, in some early tests that antedated the beginning of proteal therapy, an experimenter administered doses of one hundred cubic centimeters of sheep-blood serum into the peritoneal cavity of a cancer patient, with seemingly beneficial results. It is noteworthy that the severity of the deferred anaphylactic reaction (including chill) is by no means determined exclusively by the quantity of protein administered. It has already been noted that proteins to which the system has not been habituated, such as those of alfalfa, produce relatively strong reactions.

The second laboratory investigation, to which reference was just made, concerns the presence of uric acid in the red corpuscles. In the *Journal of Biological Chemistry,* August 20, 1915, Benedict shows that uric acid exists in the blood in two forms, in a "free" and in a "combined." Ox-blood, which, when tested by the method of Folin, hitherto considered reliable, showed a content of 0.2 mgm. of uric acid per 100 c.mm., was found as a rule to contain in reality about 7 mgm. of total uric acid per 100 c.c. of blood, practically all of this being contained in the red blood cells. "If the ox blood were allowed to stand at room temperature and protected from bacterial contamination, there was found to take place a gradual transition from the combination to the free form of uric acid, apparently due to the action of some ferment. . . . Benedict suggests that possibly the free uric acid is that which is ready for excretion as such, while the combined is capable of further catabolism." (Summary appearing in *Medical Record.*)

It must be obvious that this finding of large quantities of uric acid in the red cells gives strong support to that part of the proteomorphic theory which postulates the red cells as the seat of the enzymic activities which accomplish the ultimate decompounding of the protein by-products. Uric acid is one of the most important of these by-products. It chances to be one that can ultimately be eliminated by way of the kidneys; but whether the red cells excrete it into the blood for that purpose, or whether it merely is left in the blood stream when the red cell is disintegrated in the liver, is still conjectural. Meantime Benedict's experiments give additional evidence that the red cells have precisely such enzymic functions in connection with the later stages of decompounding of the protein molecule as the proteomorphic theory postulates.

Possibly a few words of further exposition and interpretation may be desirable, illustrating a little more in detail the chemical aspects of the observed facts in connection with the suggested explanation along the lines of the proteomorphic theory.

Note, then, that the chemical formula of uric acid is $C_5H_4N_4O_3$. Obviously we have here a substance not distantly related to some of the amino-acids, but proportionally richer in nitrogen than any one of these, the only one approaching it in this regard being arginine ($C_6H_{14}N_4O_2$). Another significant distinction between uric acid and amino-acids is the fact that it contains three atoms of oxygen and only four atoms of hydrogen. There is no amino-acid with less than five atoms of hydrogen; and all but three of them have either two or four atoms of oxygen, each of the three exceptional ones having only a single atom of nitrogen.

We have, then, in uric acid a compound relatively rich in nitrogen and oxygen, but poor in hydrogen. To modify it by adding a molecule of water would probably (in view of the four atoms of oxygen) give it extreme instability; and to take a molecule of water away from it would deplete its hydrogen supply, which is already below the minimum amino-acid standard. Uric acid, therefore, appears to represent an end product of the split protein molecule of such structure that it does not afford available material for the making of amino-acids—the only form of nitrogenous building material that the system can utilize in its synthetic operation. This applies, at any rate, to the portion of uric acid which finally appears in the blood plasma. The red blood corpuscle does, apparently, modify a part of the original uric acid supply, since only a fraction of it appears in the plasma.

Similar reasoning applies, seemingly, to those other waste-products of protein metabolism, urea (CH_4N_2O) and bilurubin ($C_{16}H_{18}N_2O_3$); each with an odd number of oxygen atoms; one hopelessly deficient in carbon atoms, the other with an excess of them. The origin of bilurubin as a product of the destruction of red corpuscles in the liver has long been known; and as a matter of course, it received consideration in the development of one important aspect of the Proteomorphic theory. That the observations linking uric acid with the red corpuscles were made subsequently to the putting forth of the Proteomorphic theory, and quite independently, gives them added value as corroborative of the truth of the theory itself.

Meantime, as throwing light from another angle, we may recall experiments made thirty years ago by Horbaczewski, which showed that uric acid was formed during the digestion of spleen pulp with blood in the presence of oxygen, but that in the absence of blood only the purin bodies hypozanthin and zanthin were formed; the so-called zanthin oxydase requisite to complete the transformation into uric acid being apparently lacking. It seems a plausible inference that the corpuscles supply this oxydase, since the presence of blood was the determining factor in bringing about the final oxidation through which zanthin, $C_5H_4N_4O_2$, is transformed into uric acid, $C_5H_4N_4O_3$.

This observation, linked with the new revelations of Benedict, above cited, makes plausible the further assumption that the red corpuscles (found thus, apparently, to have an essential share in the genesis of uric acid from purin bases, and demonstrated as the chief locus of uric acid after it is formed), are the source also of the uricase that transforms uric acid (by removal of a molecule of the carbonyl group, CO, and the substitution of a molecule of H_2O) into allantoin, $C_4H_6N_4O_3$; and in due course

effects the hydrolysis or oxidation of each molecule of allantoin (by removal of two molecules of CO_2 and substitution of a molecule of H_2O) into two molecules of urea, CH_4N_2O, the ultimate waste product of purin-bearing proteins.

If this assumption is valid, a still clearer view is gained of the *modus operandi* of non-specific proteins as therapeutic agents in dealing with rheumatoid conditions (commonly believed to be associated with the inadequate catabolism of purin bodies and their oxidation product, uric acid), and with malignant neoplasms, the structure of which is largely made up of purin-bearing proteins. An agent which stimulates production of red corpuscles and enhances their enzymic activities, as the non-specific proteins have been amply demonstrated to do in my hands and those of my associates, should theoretically be effective in precisely those conditions in which the proteals have been observed to have clinical value.

Further consideration of this aspect of the subject must be deferred, however, until we have dealt with the more general fundamental properties concerned. Taking up the sequence of the original presentation of the Proteomorphic theory, we may advantageously make inquiry as to the extent to which foreign proteins are present in the parenteral system under usual conditions.

Proteolytic Activities of the Leucocyte

It has been shown by various experimenters (Voit and Bauer, Haidenhain, Friedlander, Waymouth Reid, Ascoli and Vigano) that, under certain conditions, unmodified food proteins may find their way through the intestinal walls and enter the general circulation. It is against these, according to the present view, that the digestive functions of the various types of leucocyte are exercised; the work of the leucocyte with these, as with the bacterial proteins, being a work of proteolysis strictly comparable to that performed by the digestive ferments in case of proteids in the digestive tract—with certain variations to be noted.

This view finds strong support in the fact that one at least of the enzymes found in the body of the leucocyte is closely comparable to, if not identical with, the trypsin of the digestive canal. It is possible, according to some experimenters, that synthetic activities also lie within the capacities of these enzymes (all catalytic phenomena are conceivably reversible). But, assuredly, their habitual province is to break down or cleave this protein molecule, not to synthesize it.

It is known that the unbroken food protein, and even so small a cleavage product as peptone, do not exist normally in the

blood stream. The peptones of the digestive canal are believed to be further hydrolized, with the production of amino-acids, in their passage through the intestinal wall. The leucocyte accomplishes the same cleavage (or at all events the early parts of this cleavage) in the case of foreign proteins that come to it. And the quantity of these is sufficient to give full scope for the leucocytic activities; for experiments show that the intrusion of the unbroken protein molecule must be an extremely common incident, even if it cannot be considered a strictly normal one. Moreover, there are complications involved in the task of disposing of these unwelcome visitors.

The first of these complications is contingent on the fact that the leucocyte is thus called upon to deal with large protein molecules of many types, and that it can scarcely be supposed to be able to do so without producing toxic cleavage molecules at some stage of the process that may escape from its substance—say through dissolution of the body of the leucocyte itself—and contaminate the blood plasma. Even though the original protein was in the form of a wholesome foodstuff, say protein of beef or of egg or of milk, there is always possibility that in its decompounding there may arise combinations of molecules that are poisonous to the tissues of the organism.

As Vaughan phrases it, there is a poisonous group in every protein molecule.

Possibly it would be correct to say that there are many poison groups; but Vaughan finds that their physiological effects are essentially the same in all proteins. He has attempted to isolate this group of molecules which, in its free state, becomes a poison (so he believes) on account of the avidity with which it disrupts other protein molecules. In the purest form in which he has been able to isolate this group (and this is probably, he conceives, far from chemical purity), it kills guinea pigs of from two hundred to three hundred grams weight, when injected intracardiacally in doses of half a milligram. In the original protein molecule, it is held, the poisonous group is physiologically inert, because it is combined with secondary groups called side-chains. But these secondary groups are detached or decompounded in the proteolysis of the molecule; and there is conceivable danger that during this process the poisonous group may become detached and, diffusing in the blood stream, exert a toxic effect on the central nervous system. There are no observed phenomena associated with the therapeutic parenteral introduction of the proteins that suggest this, however, unless the anaphylactic reaction occasionally induced be so interpreted.

The danger of such a result when proteins are digested in the alimentary tract is small, because the poisonous group is prob-

ably not readily absorbed through the intestinal wall. But the leucocyte itself is suspended in the blood stream, and it must on no account permit the formation of a poisonous group, or if such is formed it must be retained within the substance of the leucocyte until it is further transformed and rendered innocuous, or is otherwise guarded (for example by the red corpuscles) or extruded from the blood stream.

Something as to what this implies may be conceived from an attempt to visualize the protein molecule, even in the vaguest way. A typical protein, for example, is globin, the basis of hemoglobin. Plimmer gives this formula for globin: C_{726}, H_{1174}, $N_{194}S_3O_{214}$. In the process of digestion, this enormously large and complex molecule undergoes hydrolytic cleavage again and again. A single molecule of protein thus cleaved (always in such a way that each new molecule contains a modicum of nitrogen along with the other elements) makes up successively molecules of proteoses and of peptones and polypeptids, and ultimately, if the cleavage is carried far enough, the disintegrated fragments constitute the relatively simple amino-acids, which form the building stones of all proteins, and of which almost a score of different types are now known, a few of which have become reasonably familiar in recent medical literature under the names of glycine, alanine, valine, leucine, tyrosine, etc. The simplest of these, glycine, has the formula $C_2H_5NO_2$; but the others are not much more complex; leucine, for example, being fairly typical, with the formula $C_6H_{13}NO_2$.

It will be seen that something like two hundred molecules of the amino-acids—each with its single atom of nitrogen—would result from the final cleavage of a single ordinary protein molecule. So the digestion or proteolysis of even a small group of protein molecules is like the tearing to pieces of a building composed of many thousands of individual bricks, stones, and timbers. It is obvious that the task thrust upon the leucocytes by the intruding protein molecule is by no means a simple one. Yet there is abundant experimental evidence that such proteolysis of an invading protein does take place parenterally; and to the present writer, at any rate, it seems highly probable that it is the blood corpuscles, rather than any of the more specialized tissues, that perform this function.

The fact that only small quantities of foreign proteins, if experimentally introduced into the blood stream, are transformed (the major part being excreted by the kidneys unchanged), is obviously consonant with the relatively small bulk of the leucocytes in their totality, as above referred to.

To be sure, there do remain residual molecules, after final

cleavage is effected, that are actually toxic—though not in the same degree as the artificially produced product of Vaughan. These are the familiar end products uric acid, urea, and creatinine—substances with which the body has learned to cope by bringing about their early elimination. Save for this small residual portion, the protein molecule will have been transformed into amino-acid foodstuffs which, we may suppose, do not differ in any essential particular from those supplied in far larger bulk from the usual digestive-tract proteolysis of the proteins, including the stages of dismemberment effected in the walls of the intestine itself during absorption.

So much has been said about the toxic molecule elaborated in the course of protein hydrolysis in Vaughan's laboratory experiments that it is desirable to call attention to the fact that this is an artificial product devised by special manipulation. The possibility that similar toxic molecules are developed in normal proteolysis of the protein molecule has been considered above. But experience shows that if such toxic molecules are indeed developed, short of the familiar end products (of which there is no evidence), they are handled in such a way as to shield the system against untoward consequences. The entire therapeutic procedure under discussion in the latter part of this volume (namely, Proteal therapy) is based on the hypodermic injections of foreign proteins. Toxic results (aside from a temporary anaphylactic reaction) have not been observed.

Moreover, in experimentally testing the Proteals I have administered vegetable proteins of many types hypodermically to small (400 to 800 gram) guinea pigs day after day in doses of 20 to 30 milligrams, with no harmful effects whatever. The animals thrive under the treatment, proving conclusively that there are no toxic molecules developed in the natural hydrolysis of these vegetable proteins with which their corpuscles (or other tissues) cannot adequately cope.

It should be recalled, however, that the proteins with which these therapeutic tests and animal experiments are made all have their origin in vegetables not far removed, botanically, from food plants, and hence are relatively non-toxic. This, however, does not greatly change the argument, since (as above stated) Vaughan liberates his toxic molecule from various types of protein indifferently. From the standpoint of practical therapeutics, so far as present evidence carries us, this toxic molecule is a negligible quantity in non-specific protein therapy. The administration of the Proteals day after day, for a term of months, to patients who improve steadily in blood conditions and in general health, sufficiently establishes that important point.

The Leucocyte and Bacterial Proteins

But the task of the corpuscles in shielding the tissues against the intrusion of unwelcome proteins in non-assimilable form becomes enormously complicated when the proteins in question are of unfamiliar types and are encased in protective cell walls —in other words, when they make up or enter into the bodies of bacterial invaders. As already pointed out, however, the capacity of the leucocyte to engulf these bodies and to digest them and make them part of its own substance is not at all a matter of theory, but a matter of observation under the microscope.

According to the present view, there is no fundamental difference between the digestion of the bacterial proteins and of any other type of protein—say a morsel of muscle. There are practical difficulties to be solved, such as getting through the cell wall of the bacterium, but the transformation of its protein, through cleavage, into amino-acids is a process of the same general type as any other proteolysis.

As qualifying this statement somewhat, however, it should be borne in mind that no two proteins from different sources—from the bodies of different species of animals for example—are identical as to all their groupings of molecules. Dr. Nuttall's remarkable precipitin experiments show how marvelously the specificity of proteins holds throughout the animal kingdom. The highly interesting demonstration in the transplantation of organs from one animal to another made by Dr. Alexis Carrel evidence the same thing from a quite different angle. This aspect of the subject is so important, and its bearing in the ultimate problems of protein therapy is so significant, that it will be well to present here a brief review of the two groups of experiments in question.

Transplanting Organs

Dr. Carrel has shown that the lost members of a higher animal may be replaced by the substitution of a new member through a surgical procedure. He has amputated the leg of a dog, for example, and replaced the member with a closely similar one taken from another dog; and has seen the new member grow into place and become a part of the body of its new host.

Dr. Carrel has similarly transplanted various internal organs, including the kidneys, from one animal to another, and caused them to take root, as it were, and perform their normal functions. The success of his experiments is due largely to his introduction of a new method of uniting arteries and veins, whereby they are so cleverly sutured together that scarcely a trace of the point of union remains when the wound has healed.

From the present standpoint, the thing of chief interest is that Dr. Carrel's observations show that there is a specific quality about the tissues of an animal that is profound and individual. The kidney of a cat seems to perform identically the same function as the kidney of a dog. But one cannot be substituted for the other in these experiments in transplanting members. The kidney of a dog may be transferred to another dog; the kidney of a cat to another cat; but the two must not be interchanged.

Even where the organ experimented with is so simple as the tube of an artery, it is with difficulty that an exchange between animals of different species may be effected. To all casual observation, and even to close observation with the microscope, the artery of a cat seems identical with that of a dog; but there is a deep-seated chemical difference which makes itself felt if, for example, a section of cat's artery is made to replace an exsected portion of the artery of a dog.

It was a foregone conclusion, therefore, that the attempt recently made by a Berlin surgeon to replace a diseased human kidney with the kidney of a monkey would be a failure. The surgeon of the future will doubtless replace diseased kidneys and other vital organs with normal ones, but the substituted organs will be taken from human subjects—say from the victims of accidents, or from executed criminals.

Tracing Blood Relationship

The specific quality which thus pervades every tissue of an organism—so that the remotest cell of a cat, for example, has some quality of *felineness* that distinguishes it from a cell of any other species of animal—extends its mysterious influence so comprehensively that it includes not merely every fiber of the organism, but every drop of blood in an animal's body.

The proof of this has been given by Professor G. H. F. Nuttall, the American biologist, now of the University of Cambridge, in the series of experiments just referred to.

Professor Nuttall has developed a system of blood testing of such delicacy as quite to transcend the bounds of microscopic examination or of any chemical methods hitherto known; and in so doing has found a method of testing the relationships of different tribes of animals that seems little less than magical.

The tests show, for example, that man is more closely related to the old-world monkeys than to the monkeys of the new world; our closest relatives being the chimpanzee, the gorilla, and the orang in the order named. Similarly the relationships between different members of the dog family, the cat family, and the like, are traced. Thus the hyena appears to be to some extent

intermediate between dog and cat tribes, but, contrary to what might be expected, it is much more closely related to the cat than to the dog. The seal and sea lion, on the other hand, are closer to the dog family than to the cats. Moreover, the seals are somewhat more closely related to the weazel tribe than to the felines.

The porpoise, which might be supposed to be allied to the seal, is found instead to show close affinities with the ox tribe, and in particular with the pigs. Indeed the porpoise may be regarded as a pig that has taken to the water and perforce become carnivorous in diet. It is necessary also to record the rather unflattering observation that the blood of the porpoise shows more pronounced affinities with human blood than with that of most other animals.

The family groupings among reptiles show close blood relationship between lizards and serpents, and a slightly less close relationship between turtles and crocodiles. The reptiles are more closely related to birds than to mammals. The relationship appears to be particularly close between birds and turtles; less close between birds and crocodiles; the avian relationship with lizards and serpents being still more remote.

These tests singularly confirm the conclusions of the zoölogist, based on study of the anatomical structures of the different tribes of animals; but the testimony is absolutely independent, the tests being made, as already pointed out, by means of blood alone.

Indeed the maker of the test may never have seen a specimen of the species whose rank in the organic scale he is determining. The specimens of blood that Professor Nuttall used in his classical series of experiments were collected from a multitude of sources; no fewer than seventy different persons sending specimens from different parts of the globe.

Many of the collectors were hunters, who merely dipped a piece of filter paper in the blood of a quarry and transmitted it to the Cambridge Laboratory. There the discolored piece of paper was soaked in water to produce a clear solution of blood serum. A portion of this solution was placed in a test-tube, and this test-tube put in a rack along with scores of other specimens, each bearing only a number.

Into each test-tube a small drop of a certain liquid was placed. If the solution in the test-tube became cloudy, the experimenter was able to pronounce definitely that the blood was that of an animal of a certain tribe. It might, for example, be the blood of a tiger or a leopard or a panther or a cheetah; but it could not be the blood of a hyena or a wolf or a dog.

Again the test might be applied to a blood stain on a handkerchief or knife, or on a fragment of wood from a floor or

window sill, or scraped from the surface of a boot or a coin. In this case the question as to whether the stain was caused by human blood or by that of some animal might be the deciding testimony in a murder trial.

Here the method of procedure would be the same as before. A solution being made from the blood stain and placed in a test-tube, the trial fluid would determine whether the stain was due to human blood. If the test proved negative, other tests might determine what particular animal supplied the blood. In a case reported by Professor Uhlenroth, for example, a blood spot in the road, suspected to be of human origin, was found to be from the blood of a pig. In another case blood stains on a garment were reported as being partly human and partly due to the blood of the sheep. In this case it was subsequently proved in court that the wearer of the garment had committed a murder, but that he had slaughtered sheep two weeks before the murder.

How the Test Fluids are Developed

A word now as to the production of the magical fluid with which such tests are operated. The fluid consists of a portion of blood serum drawn from the veins of a rabbit. The peculiar properties of the serum have been developed by repeated injections into the system of the serum of human blood or that of some other member of the animal kingdom, according to the particular type of test that is to be made.

A rabbit inoculated with human blood develops a so-called anti-human serum. Another rabbit inoculated with the blood serum of a cat, will develop an anti-feline serum; and so for all other tribes of animals—including not merely mammals, but birds, reptiles, and even crustaceans, such as the lobster and its allies.

The explanation of the development in the body of the rabbit of the peculiar quality of blood that gives the anti-serum its value in such tests as those outlined, is found in the fact that the blood of almost any animal has a certain quality of toxicity when injected into the veins of an animal of different species. In some cases this action may be very virulent.

For example, fifteen drops of the blood of an eel injected into the veins of a dog weighing about thirty pounds may produce death in seven or eight minutes.

In another experiment ten drops of the blood serum of an eel killed a rabbit of ordinary size in two-and-a-half minutes. The foreign blood serum appears to attack the blood corpuscles, rendering them functionless and presently dissolving them.

Curiously enough the blood corpuscles of new-born rabbits are much more resistant to foreign blood than are those of the adult rabbit. But a certain degree of resistance obtains in all animals, and this may be accentuated by introducing a very small quantity of foreign blood serum, and from time to time repeating and increasing the dose. In this way the system of the animal becomes to some extent immune to the poisonous effect of the foreign blood, through development of what for want of a better term is called an anti-serum.

The blood of a rabbit that has attained this condition may then be used in testing for the presence of the particular type of blood that was used in developing the anti-serum. For example, if human blood was the kind injected into the system of the rabbit, the rabbit's blood will now serve as a test for human blood.

Man's Remote Relatives

It appears, however, that the anti-serum thus developed, while its most pronounced reactions will be given with solutions of human blood, will also react in a less marked degree with the blood of other animals.

If successive drops of the anti-serum are introduced into one test-tube after another, as in Dr. Nuttall's experiments, it will be observed that in some tubes there is an immediate reaction, resulting in a white precipitate. In other tubes the reaction will set in only after some minutes; in yet others after hours; and the remaining test-tubes will remain permanently clear. It is these graded results that enable the experimenter to test the blood relationships of the different animals.

It is found, for example, that when a test is made with human anti-serum, an immediate reaction is observed only in test-tubes containing human blood. Less prompt and less marked reaction occurs in the tubes containing the blood of the man-apes; still milder reaction in the case of baboons, monkeys, and marmosets in succession; and a long delayed or altogether negative result in all other cases. It is obvious how similar tests with other types of anti-sera enable the experimenter to follow out the relationships of different tribes of animals.

Professor Nuttall's experiments comprised sixteen thousand individual tests, with a total of at least 586 species—mammals, birds, reptiles, batrachian, fishes, crustaceans—coming from all parts of the globe. These experiments are in themselves highly interesting; in their implications they are nothing less than astounding.

Doubtless some hundreds of thousands of years have elapsed

since the direct ancestors of men branched from a common stem with the direct ancestors of the gorilla. There has been no blending of blood in the intervening centuries. Cats have been cats and dogs dogs from geological epochs so remote that we hesitate to guess their span in terms of years. So the intimate chemical qualities that denote man or ape or cat or dog, each in contradistinction to all the others, must have been transmitted unmodified through countless thousands of generations.

It taxes credulity to believe that such intangible properties could be transmitted unmodified through the blood streams of such myriads of individuals; but the evidence of the test-tubes proves that this has been done.

What makes the marvel greater is the fact that the bodies of the animals have meantime been so modified as to develop utterly divergent species—for example, the lion, the tiger, the puma, the leopard, and the house cat; different types of dogs, wolves, foxes, and their allies. But in each case some intangible quality of the blood remains unchanged to prove the common origin. Blood is indeed thicker than water.

The Source of Specific Antibodies

In making the above presentation of the experiments showing the specificity of proteins, I have drawn on the text of one of my popular books, *Miracles of Science*, which appeared not long before the original publication of the Proteomorphic theory. I have thought it well to present this detailed account of the precipitin experiments, because they bear so fundamentally on the essential problem of the protein response in therapeutics, the elucidation of which is the chief purpose of the present book.

These experiments make it clear that the phrase "non-specific proteins," notwithstanding its convenience, is in the final analysis a misnomer. Proteins may be used non-specifically, but no two are precisely alike. Making present application of this principle, and recalling that the single enzyme trypsin is observed to begin the digestion of many types of protein, it must be supposed that the exact steps of the successive metamorphoses are somewhat different in each case. It is even possible that there are various types of the enzymes that now go by the name trypsin, each one adapted to deal with a different protein. But this is only conjectural, as the chemistry of the enzymes is still very obscure.

Be that as it may, however, it is certain that each type of protein undergoing parenteral digestion and assimilation evokes from the digestive mechanism a unique response, which finds expression in the secretion into the blood stream of specific types

of antibodies. These specific antibodies are no mere by-products of the cleavage of the foreign proteins, as was once supposed. They are chemical compounds put forth by the defensive mechanism and having such specific properties as will enable them to antagonize the particular protein that evoked them. This is equally true of proteins of every type—of the molecules that make up the most wholesome foodstuff, no less than of those that make up the most virulent bacillus.

The chemicals in question are known as bactericides, bacteriolysins, hemolysins, agglutinins, precipitins, and opsonins. Some of these names may be duplications, but the existence of a certain number of what may conveniently be termed "antibodies," developed through response of the organism to the intrusion of the foreign proteins, is a chemical fact supported by unassailable evidence, quite apart from any theory whatever as to the precise bodily mechanism through which they are produced. We have just seen this illustrated in detail in the case of Dr. Nuttall's precipitins.

But when we attempt to localize this mechanism, we find ourselves at once involved in difficulties. To be sure, the line of reasoning just presented seems to point rather clearly to the leucocyte as the developer of the antibodies; inasmuch as that cell is known to be the digester of the offending protein itself. But if we seek direct proof, we find the evidence not altogether convincing. Nevertheless a number of observations have been recorded, as to the result of direct experiments, that are at least highly suggestive.

Thus, for example, Ruffier and Crendiropoulo, as cited by Nuttall, found evidence that agglutinins may exist in the leucocytes of rabbits and guinea pigs, inasmuch as an extract of leucocytes from an immune animal had greater agglutinating power than did the same animal's serum. The observations of Metchnikoff convinced him that the output of "fixatives" varies directly with the degree of phagocytosis. Gengou, following up Metchnikoff's conception at the Pasteur Institute, "concluded that the hemolysins are derived from leucocytes, for the reason that plasma separated from fresh blood, when cooled throughout, by centrifugalization, was less hemolytic than serum." The experiments on which this last conclusion were based were repeated, however, by Ascoli, with opposite results, and Pfeiffer and Marx found antibodies less abundant in the ground bodies of leucocytes of immunized animals than in the plasma.

Again, according to a recent analysis of Gay and Rusk, "the work of Deutsch, Castellani, Rath, Weil and Braun, and Kraus and Schiffmann all shows that the agglutinins appear in the blood serum before they are present in the extract of any organ."

But "although Gruber originally suggested that the polymorphonuclears form the agglutinins no experimental evidence goes to prove this, and the experiments of Achard and Bensaud, Widal and Sicard, of Paetsch, and of Kraus and Schiffmann all seem to disprove leucocytic or local origin."

"Sweet found that he could increase the complement-content by the injection of substances having a positive characteristic action on leucocytes." (Nuttall.)

As to precipitins there are experiments by several observers (including Cantacuzène and Swerew, Hiss and Zinsser, and Stenstrom) seeming to point to the leucocytes as a definite source; and Kraus and Schiffmann "emphatically regard the blood as the source of precipitins." Here again there is contradictory evidence; but, on the whole, it may be said that a strong case is made out for the leucocyte as the source of precipitins and agglutinins, and a somewhat less convincing case for bacteriolysins and hemolysins. I shall have occasion presently to refer more at length to some recent experiments of J. W. Vaughan, in which antibodies evoked by cancerous tissues were definitely located in the large mononuclear leucocytes.

Meantime it is to be noted that a considerable number of the workers who failed to localize the immune bodies in the leucocytes found evidence for their localization in one or another of the leucocyte-forming tissues—the spleen, the lymphatics, and the bone marrow. Thus, according to Nuttall, "Shibayamia found hemolysin for dog corpuscles in the spleen and lymphatic glands of normal guinea pigs, not elsewhere."

Again Gay and Rusk interpret the work of Pfeiffer and Marx as seeming "to indicate very clearly that the protective antibodies directed against the cholera spirillum are elaborated in the leucopoietic organs, particularly in the spleen, but to a less extent in the bone marrow, inasmuch as extracts of these organs protect guinea pigs from infection before the blood serum does. Deutsch essentially corroborated these findings with B. *typhosus* and Castellani with B. *dysenteriae*. . . . These authors agree that the spleen is not essential, as its removal at best but slightly inhibits antibody formation; the bone marrow and lymph nodes are secondarily concerned."

As to hemolysins, we find this comment: "Among the fixed tissues, the liver and spleen seem to have shared the honors as the possible sites of hemolysin formation. Leuckhardt and Becht, following the work of Hektoen and Carlson, found that the spleen alone of the organs of a dog that has received goat or rat corpuscles 24 hours previously has the property of immunizing new animals." But this experiment is not considered con-

clusive. "Carrel and Ingebrister have produced hemolysins in the growing embryonic spleen." As to agglutinins, it is noted that "there is some evidence of agglutinin formation in the spleen offered by V. Emden, Jatta, and Girgoleff."

All this is interesting; but there are contradictory experiments all along the line, and Gay and Rusk do not regard the evidence on the whole as conclusive. They say, however, "there seems greatest agreement on the point that antibodies are formed either by the leucocytes or the leucocyte-forming organs. And yet a good deal of recent work points with increasing emphasis to the liver, an organ which, in view of its other functions, might logically likewise serve to produce antibodies.

It will appear that the conflicting testimony is largely harmonized so soon as we take account of the red corpuscles along with the leucocytes and cytogenic system. For the moment, however, it suffices to point out that all the different experimenters are at one in designating either (1) the leucocyte-forming organs, or (2) the leucocytes themselves, or (3) the liver, as the probable sources of the origin of antibodies. As to the liver, I now call attention to the fact that this organ is the seat of destruction of great numbers of red blood corpuscles; and that its fluids are very freely supplied with leucocytes, some of which come to it directly through the portal vein after their apparent origin in the spleen. It has even been suggested (by Sajous) that the eosinophiles may be formed in the liver.

All in all, it may fairly be said that the experimental evidence raises at least a strong presumption in favor of the belief that the lymphoid tissues that develop the leucocytes, and the leucocytes themselves, are closely associated with the processes through which certain types of antibodies are developed. The antibodies in question, according to the Proteomorphic theory, are the "complement" and sundry bactericides, bacteriolysins, agglutinins, opsonins, and precipitins—in a word, the antibodies evoked by antigens composed of unbroken proteins, including, of course, the bodies of living and dead bacteria.

If the direct evidence for this part of the theory is not absolutely demonstrative, at least it may be said that there are no experiments that clearly contradict it. Meantime, it is worth while to inquire whether the general relations of the leucocyte and its parent cells, viewed in the evolutionary scale, are such as to justify the assumption that they perform the particular functions here ascribed to them. Such a discussion could, of course, have no force were it contradicted by direct experimental evidence; but it may have confirmatory value when its findings seem to accord with those of the experimenters.

The Primordial Leucocyte

In such a view, it would appear that the leucocyte is a relatively unspecialized cell, the least-modified present-day representative of the prototypal single-celled ameboid organism from which the entire body has developed. It is consistent with this view that the leucocyte should have retained the primitive functions of digestion and assimilation of proteid bodies as its essential task in the developed body.

It is not unlikely, then, that in reviewing the conditions which determine the relations of the protozoan to its environment we may gain an insight for the better interpretation of some of the activities of the leucocyte, its lineal descendant.

If, then, we go back to the evolutionary beginning, and review in imagination the conditions of the time when the only living organisms were single-celled ones, we must think of our primordial ancestor as a protoplasmic cell endowed with a curious capacity to absorb certain materials from the environment, and through assimilating them to grow; endowed, also, in the pursuance of this mission, with capacity to respond to impressions received from the environment.

The protoplasm making up the body of this primitive organism was a compound of carbon, hydrogen, oxygen, and nitrogen, with minute quantities of a few other chemicals, notably sulphur; which was liquid in character, but differed in its essential qualities from the inorganic substances about it, chiefly, we may suppose, because of the exceedingly intricate character of the relations of the very large number of atoms that entered into each molecule. The physical principles that determined the relations of this protoplasmic solution with other solutions in which it might be immersed were determined in accordance with the laws of capillary absorption and of osmosis.

The essential functions of the protoplasm, in virtue of which it might be spoken of as a living organism, were probably contingent on the fact that each molecule contained a large number of atoms of carbon, an element having four chemical valences; and a considerable number of atoms of nitrogen, an element that may have either three or five valences, and which is signally characterized by its unwillingness to enter into combination, and, contrariwise, its exceeding desire for liberty when once it has been combined, resulting in the instability of all nitrogen compounds. Nearly all explosive compounds, it may be noted, contain a nitrogen element. Indeed, the analogy as to composition, between protoplasm and dynamite and other high explosives, is striking and highly suggestive. There is one important difference, however—artificial explosives contain enough oxygen to

burn their other constituents; whereas the protein molecule, in order that it may not be too unstable, is provided with a comparatively small supply of oxygen.

Recall now the principles of osmosis, as revealed by the studies of Van't Hoff. It appears that osmosis, or the passage of liquid through a membrane from one solution to another, is due, not to any suction principle, but to the pressure on the membrane exerted by the molecules of the denser liquid; that is to say, the liquid which has the larger number of free molecules in a given volume.

A single liberated atom or ion of oxygen or any other element is the osmotic equivalent of the most gigantic protein molecule.

This is the curious fact discovered by Van't Hoff, and substantiated through the researches of Arrhenius and Ostwald. It is of fundamental importance in its application to the relations of the living cell.

Suppose, for example, that a full-sized protein molecule in the protoplasm of a living cell were suddenly to be disrupted into molecules of its component substances, the amino-acids. Immediately the osmotic pressure exerted by the molecule would be increased a hundred fold. The pressure might disrupt the cell. Short of that, it would result in pressing the cell wall outward against the surrounding fluid, with the result that a certain amount of that fluid would pass through the cell wall and become a part of the cell content. Suppose, then, just as equilibrium of pressure between the cell and its surroundings is reestablished, there is a recombination of the dissociated elements to produce full-sized protein molecules. A hundred or so amino-acid molecules becoming a single protein molecule, the osmotic pressure in the cell would be correspondingly reduced, with the result that the cell would contract under stress of outside pressure and exude a portion of its content.

It is not unlikely that this process may explain the enigmatic action even of such highly developed cells as the muscle cell in the animal body, the contraction of which has never been clearly understood.

I am not unaware that some physicists have denied that the laws of osmosis apply to colloidal substances. But, aside from the *apriori* improbability that these liquids defy the operation of so fundamental a law, the balance of evidence seems corroborative. And, as regards the particular application in hand, there is, I believe, no alternative hypothesis that explains muscular action so satisfactorily. A decompounded molecule of muscle-cell protein becomes, let us say, one hundred molecule of amino-acids; and the osmotic pressure within the cell is increased a hundred fold. The swelling and hardening of the muscle, with

associated contraction due to the arrangement of the cells in the muscle-fiber sheath, is the tangible aggregate result. When the amino-acid molecules are recompounded into larger protein molecules, their number and consequently their osmotic pressure are correspondingly reduced, and the muscle relaxes.

Whatever the force of this parenthetical suggestion, however, it is certain that osmotic action explains many of the fundamental processes of assimilation. It should be added, however, that in a comprehensive view, the character of the cell wall itself must not be overlooked. The permeability of this is an important consideration; and it has been found that the nature of the medium in which it lies, notably with reference to mineral salts, may greatly modify this permeability. At the moment, however, this aspect of the subject need not be examined in detail.

It is obvious that our primitive bit of protoplasm, under the shifting conditions of osmosis, expanding and contracting as portions of its protein content are dissociated and re-formed, may have acquired, by virtue of this principle alone, a certain function of primitive motion. Granted a group of unstable carbon-nitrogen compounds encased in a cell wall, we have a primitive organism which may manifest the fundamental conditions of assimilation and excretion.

The precise chemical composition of the cell-content making up the body of this living organism, in connection with its fundamental proteins, will depend upon the chemical composition of the medium in which it lives, and from which it absorbs matter, and into which it excretes residual matter. And in any case in which the mechanism of absorption and excretion of a given cell-laboratory has reached a status of equilibrium, the intrusion of any new chemical substance into the medium must serve as a disturbing element.

Suppose that this disturbing element takes the form of another organism, which has been accustomed to a different medium, and hence which has developed a somewhat different chemical composition, to the extent at least of modifying the side-chains of its protein molecule. Then, in the nature of the case, there must be a certain antagonism between the two organisms. Each, through its excretions, modifies somewhat the character of the medium, and makes it in a sense an abnormal medium for the other. Unless both organisms are able to modify somewhat their previous mode of existence, finding a way either to assimilate or to neutralize the abnormal elements now introduced into the medium, they cannot survive.

If either of them does survive, that fact is proof positive that the organism in question has found a way to adapt itself to the new conditions. It has so adjusted and modified the

regular routine of its internal chemical processes, that the excretions of the other organisms are no longer noxious to it. If we choose, we may say that the organism has developed autobodies or antitoxins against the offending neighbor organism. Thus it would appear that the production of such antibodies must be one of the most fundamental and primordial of life processes. It is a function that is retained throughout the history of all descendants of the protozoan, even to the remotest cell of the highest organism.

The reason for this is not far to seek; for it is a familiar axiom of the evolutionist that all life is a struggle; and it is obvious that the developing organism must come constantly in contact with other organisms. With each new one, the old struggle must be renewed with slightly new aspects, and new methods must be found to equalize the adverse conditions introduced.

As the organism evolves to a multi-cellular condition, and develops the various members and organs that mark the higher animals, it will pass constantly to new environments and come in contact with new enemies. Every time it encounters a new type of food, be it vegetable or animal, it will present a new problem to its chemical laboratory of the digestive and the assimilative system. And unless this chemical laboratory proves adequate to the new task put upon it, the organism will die.

It follows that every existing organism has been able to run this gauntlet and to find a solution of the new problems presented to it.

In other words, every existing organism has learned to digest and assimilate a great variety of proteins; developing mechanisms for neutralizing their poisons, until foods that were toxic have now become wholesome.

In this view, it will be observed, there is no suggestion that one kind of protein rather than another is poisonous. It is simply that each specific type of protein is somewhat antagonistic to organisms composed of any other type of protein. It is only a cannibalistic protein diet that can be said to be intrinsically harmless. But cannibalism involves the penalty of probable race extinction; and so in the nature of things evolutionary all living organisms have learned to feed on the protein of other races of organisms, adapting their own metabolic processes until they are able to deal effectively with the offending side-chains in the foreign molecule. Such a process of adaptation requires time, and we may take it for granted that foreign proteins are "wholesome" to any given organism somewhat in proportion to the length of time during which the ancestors of that organism have been accustomed to ingest it. That any given protein food is

observed to be non-toxic is in itself proof positive that the organism is equipped with an immunizing mechanism adapted to deal with the specific minor combinations of atoms that make up the side-chain components of its protein molecules.

Nor does this apply exclusively to the proteins that we commonly think of as foods. It has equal application to the microscopic proteid organisms. Thus bacteria are relatively harmless if they are so abundant that the organisms of our ancestors have dealt with them generation after generation; contrariwise, they are classed as toxic if they are comparatively rare, so that the race has not developed a defensive mechanism against them. Note, by way of illustration, that measles is a mild disease in Europe and America, but becomes a very virulent one in Japan The presumption is that the germ of measles did not come in contact with the ancestors of our race until a period subsequent to that in which the Japanese stock had branched from the western stock.

There is abundant evidence to show that any inherent habit of action once fixed on a living organism is a perpetual endowment, to be transmitted from one generation to another in perpetuity (subject, in case of recently acquired characters, to elimination in a certain proportion of the progeny through Mundelian inheritance). So we may safely assume that when an organism has learned to deal with any given protein in such a way as to render it innocuous, the descendants of that organism will retain the capacity to repeat the process indefinitely. It follows that every higher organism can deal effectively—under proper conditions and in restricted quantities—with all the different types of proteins that have come in regular contact with its ancestors to the remotest generations.

Thus is explained the familiar fact that each higher organism can find nourishment in a great variety of foods; coupled with the fact that the blood plasma of the organism normally contains the antidotes for a considerable number of bacterial poisons.

Of course this higher organism has become a very complex mechanism, with many members, each specialized to perform a particular function. As regards this function of combating the noxious forces of the environment, the digestive system is preeminent. But this system, in the broad view, is not so much an inherent part of the organism, as an outer wall of defense so placed as to make sure that in general no unmodified proteins shall find their way through the mucous membrane fortifications. But the organism cannot depend absolutely on this defensive mechanism, as we have just seen; so it is necessary to have other defenders on guard inside the walls. And it seems on its face a plausible suggestion that the cell which retains most of the

character of the primitive primordial protozoal ancestor, and which, so far as we can see, is not specialized to perform any other function, is the one which has retained pre-eminently this primordial capacity of harmonizing the organism with the living, or, once living, elements of its environment.

Such a primitive cell is found in the leucocyte. No other cell in the body retains so fully the primitive characteristics of the protozoal ancestor. And, patroling everywhere the blood stream which carries particles ingested from the outer world, the leucocyte is most favorably situated to come immediately into contact with intruding substances, and to take up with the least possible loss of time the work of so modifying them that they meet the needs of the organism.

The leucocyte looks like an ameba, and it is seen to ingest solid particles of food just as an ameba does. Can we doubt that its chemical processes of digestion are closely comparable to those of its prototype?

The Leucocyte as a Microcosm

At the first thought, it might seem to strain probabilities to the breaking point to suggest that a cell of such proportions as the leucocyte could conceivably be the habitat of a series of chemical substances so complex and varied as is here implied. But a very brief consideration of the facts as to the size of molecules and atoms, as placed at our disposal by the modern physicist, dispels any such doubts.

It is known that the smallest particle visible under the microscope is about one fifty-thousandth of a centimeter in diameter. Cubing this number, we find that a cubic centimeter will contain one hundred and twenty-five thousand billions of such particles. But the researches of Rutherford, who has somewhat accurately determined the size of the atom, show that a cubic centimeter of space may contain twenty billion times that number of helium atoms.

In other words, the smallest particle visible under the microscope is large enough to contain many times twenty billion atoms; inasmuch as the atoms computed by Rutherford were in the gaseous condition, and hence very much more widely separated than those in the solid particle under the microscope.

It appears, then, that if we were to assume that there are one thousand different antibodies developed in the organism—each one antagonistic to some specific type of protein—there is ample opportunity for such a collection of antibodies in the smallest particle of matter visible under the microscope, even if we assume that each one of these antibodies is made up of at least twenty

million atoms. So even if the leucocyte were far smaller than it is (for, of course, it is by no means at the limit of microscopic visibility), its nucleus might be a very intricate structure indeed, chemically considered—a chemical laboratory quite elaborate enough to generate all the different types of antibody that the system could conceivably require.

Each of these nascent antibodies, as lodged in the leucocyte, may be supposed to represent a specific protein, capable of taking to itself the right combination of atoms to increase in size and, under proper conditions, to multiply indefinitely, to meet the needs imposed by the intrusion of a particular type of toxic protein. In the ordinary course of events, doubtless, only a comparatively small number of the different types of antibodies in the equipment of the leucocyte laboratory would be called upon to come into action at a given time. It might even happen that for long periods of time, even for generations, a particular type of nascent antibody that has been developed in the cell might not be called upon to meet and antagonize its specific antigen.

But what we know of the germ-cell, and of the possible quiescence of hereditary factors for successive generations, teaches us that it may readily be possible for the cell to carry forward during an indefinite period such unused increments of nascent antidotes; and yet to call them into action when the proper stimulus comes, even though such stimulus has not hitherto been applied for many human generations.

In this view, then, we may think of the cells that generate the leucocyte as a storehouse in which minute quantities of large numbers of different types of proteins are arranged, in what may be called the nascent state, all of them with potentialities of development, and a certain number of them constantly called upon to meet the stimulus of external conditions in the form of different types of protoplasms or proteids that, but for their aid, would be poisonous to the organism in the blood stream of which their daughter cells, the leucocyte, are liberated.

It is, of course, the mother cells, in bone marrow and spleen and lymph node, that must be thought of as the permanent source of supply of these nascent antibodies. For, of course, the developed leucocyte, once it has gone out from the parental abode, is in a sense an independent organism, lying beyond the bounds of the cellular system of the complex organism in the blood stream of which it operates. The force of this view is very well illustrated in the familiar fact that when toxic bacteria are ingested by a phagocytic leucocyte, these toxic bacteria are no longer able to exert a malignant influence on the organism. For a time they retain their normal form and appearance; but the leucocyte, by

engulfing the intruder, has given entire protection to its human host.

Let it be further recalled that this probably would not be true of any cells other than the leucocytes in the entire organism.

This fact, taken by itself, gives strong corroboration to the thought that the leucocyte is primarily and fundamentally a detached organism, acting in close alliance with the animal body, but being in a broad sense independent.

Of course, the same line of reasoning applies in considerable measure to the red corpuscles as well. And, in both instances, the general idea under consideration finds strong support in the fact that the blood corpuscles of different mammals are histologically so similar as to appear practically identical under the microscope. Place a drop of guinea-pig's blood, for example, and a drop of human blood, under the microscope, and not even the trained hematologist can distinguish one set of corpuscles from the other. Even as regards the numerical count, there is striking similarity in case of the red corpuscles; and the modifications in leucocyte count, aggregate and differential, are such as may readily be accounted for by long-established minor difference of dietetic habits—modifications, moreover, that may be brought into strict conformity by fluctuations in the human leucocyte count under conditions of slight abnormality.

Obviously, such conformity of corpuscular population in the blood of mammals widely separated in the evolutionary scale, suggests functions of very general and fundamental character, responsive to environmental conditions universally distributed—for example, foodstuffs substantially the same, and bacterial invaders absolutely identical.

In this comprehensive view, then, we shall do well to get away from the notion of virulent bacteria, and to think of all the stages of assimilation and immunization as closely allied, and as applying to proteins in general. In practice we must recognize the virulence of certain types of bacteria; but we shall do well to understand this virulence as conditioned merely on the fact that the organism has come somewhat rarely in contact with these particular microbes. There are myriads of bacteria always in the organism and these for the most part are as innocuous as flecks of albumin, for the simple reason that they have been so long with us that they have become domesticated—that is to say, the body-tissues have become immunized against them.

According to the Proteomorphic theory, as we have seen, such immunization has resulted in part from the activities of the leucocyte, through which the blood plasma has come to be constantly permeated with antidotal chemicals.

Antitoxins and New Chemical Problems

There are certain types of these antidotal chemicals, however, to which we have hitherto given scant attention. These are the so-called antitoxins which are developed in the blood not necessarily because of the presence of proteid bodies, but in response to toxins that are themselves the product of protoplasmic activity. No organism can grow and develop without giving out waste products that are poisonous to living protoplasm; and the bacterium is no exception to the rule. So when it finds access to the human system, it necessarily vitiates that system with its waste products.

We ordinarily think of these as toxic properties that are put out by the bacteria with the express design of injuring the human body. But such a view is altogether anthropomorphic and mistaken. The so-called toxins are merely either (1) waste products, or (2) enzymes put forth by the bacteria to aid its own digestive processes. But they may serve as virulent poisons to the tissues of their host nevertheless—which is highly unfortunate for the bacteria themselves, since death of their host will in many cases mean death for them also.

Of course, the bacteria that are being digested by the leucocyte give out such toxic principles, and it is necessary in overcoming them to neutralize these toxins as well as to proteolize the body of the bacterium itself. In this case, we may suppose, the leucocyte adds antitoxins to its list of responsive enzymes, along with the antibodies directly aimed against the proteid bodies of the enemy. It is possible that opsonin is such an antitoxin.

But there are also cases in which the bacteria only lodge on some surface of the body—say the throat—and use the vascular channels as a sort of sewer into which to discharge their waste products. The local injury may be very slight, the entire danger to the organism resulting from the presence of the excretory toxins, not to protein itself of any type. The colonization of the diphtheria bacillus furnishes a typical illustration in point.

In such a case, as is well known, the body may be able to produce chemicals that neutralize the toxins, thus saving the life of the human organism. Moreover, these chemicals may be produced in such excess that the blood becomes more or less saturated with them, giving the organism immunity to similar attacks in the future, at least for a time. These neutralizing chemicals are known as antitoxins. They are not necessarily poisonous to the bacteria the toxin of which led to their development. The diphtheria bacillus, for example, will grow and thrive in a medium containing large quantities of diphtheria antitoxin.

Here, then, is a type of antibody that has not been developed

directly through the parenteral presence of a protoplasmic body. And the question at once arises as to the source of this antitoxin. Is the leucocyte here as before the agent that guards the body from the insidious attack?

The attempt to answer this question has proved more puzzling, if possible, than the attempt to localize the mechanisms that antagonize and give immunity to the bodies of the bacteria themselves. Most workers in the field leave the question quite unanswered. It suffices for them that the antitoxin is produced somewhere in the body, and that it ultimately permeates the serum of the blood. But it is obvious that a satisfactory theory of immunity must give us a far more definite answer.

In the opinion of the present writer, there are data at hand that enable one to answer the question with a fair degree of definiteness. It must be admitted, however, that these data do not include unequivocal and demonstrative experiments, such for example as the discovery of the antitoxin in some specific tissues before it appeared in the blood serum. We must be content with indirect evidence. This, however, is to say the least highly suggestive, and its findings are full of interest. In my opinion, they justify the belief that the chief agents in the formation of antitoxins are the red blood corpuscles; their efforts being supplemented, however, on occasion, by the work of the leucocytes on one hand and by the various body tissues on the other.

The evidence is based very largely on experiments undertaken for a quite different purpose and having to do with the hydrolysis and synthesis of proteids. In particular the work of Emil Fischer and his pupils has given the clue, although, so far as I am aware, no one had attempted to interpret or follow it up until this was done in my original presentation of the Proteomorphic theory in *American Medicine* of October and November, 1914.

To gain an inkling of the import of this work, in the present connection, we must very briefly summarize some of its important findings as to proteolysis. The most significant of these experiments, from the present standpoint, are those in which Abderhalden has tested the capacity of enzymes excerpted from different bodily tissues to hydrolyze various synthetic polypeptids. The polypeptids were so named by Fischer to indicate their relationship with peptones. It is believed that the peptones (as hydrolyzed from protein through the medium of proteoses) consist of a chemical aggregation of various polypeptids. Stated otherwise, polypeptids would result from the cleavage of peptones; although in point of fact those experimented with were synthesized in the laboratory by the combination of various amino-acids.

The simplest polypeptids (di-peptids) result from the union of two amino-acids; more complex ones from the combination of three or four or five amino-acids. The molecule of a polypeptid is, therefore, complex as compared with the molecule of an amino-acid; but, on the other hand, it is relatively simple as compared with the molecule of peptone. In other words, a molecule of peptone could be cleaved, perhaps by successive stages, to form a goodly number of molecules of the most complex polypeptids yet synthesized.

It is important to get clearly in mind this position of the polypeptids as nitrogenous compounds, which are considerably more complex than amino-acids, and yet very simple indeed as compared even with peptones, which in turn have but a fraction of the complexity of the original protein from which they are hydrolyzed. There are some thousands of atoms in a molecule of protein; some hundreds in a molecule of peptone; some scores in a molecule of the more complex polypeptids; and, as we have seen, less than two dozen in the molecule of an average amino-acid.

It is familiarly known that the giant protein molecule which comes into the stomach as the chief constituent of proteid foods is hydrolyzed and disintegrated to the peptone stage (*via* proteoses) by the enzymes of the digestive tract. Just what happens to the peptone after it is absorbed into the intestinal wall has been a matter of dispute. There is no question that it is further metamorphosed, for it does not appear as peptone under normal conditions in the blood stream. The balance of authority lends strong support to the belief that the peptone is further hydrolyzed in the intestinal wall, until its molecules reach or approximate a degree of smallness that makes them available for the use of the various body-cells to which they will presently be carried by the blood stream. It seems highly probable that they enter the blood as amino-acids, of various types, and are thus carried to the tissues as dispensers of building materials, among which each individual type of cell may select in accordance with its needs—for the different body proteins are made up of different combinations of amino-acids.

But we have seen in our earlier discussions that it happens on occasion that portions of the proteins taken into the stomach find their way through the intestinal wall unmodified, or not greatly modified, by the digestive ferments, and introduce a complication in the problem of assimilation; a complication which, according to our thesis, is met by the activities of the leucocyte. If the gigantic molecule of protein thus finds its way on occasion through the intestinal wall, it seems plausible to suppose that the comparatively small molecules of the polypeptid order

must make similar entrance into the blood stream even more frequently. But if such is the case, we may fairly assume that means will be found there to effect further hydrolyses in the fluids of the body. And, in point of fact, experiments have shown that when certain polypeptids are artificially introduced into the blood stream of animals, they may fail to appear in the excretions, proving that they have been metamorphosed in the body. Abderhalden found that a considerable number of the polypeptids might thus be utilized by the organism of a dog.

Obviously, then, there may be developed within the body tissues or in the blood stream enzymes capable of hydrolyzing the polypeptid molecule—a molecule, be it understood, which the combined juices of the stomach and pancreas and duodenum, under ordinary circumstances, are unable completely to cleave or break down.

The interesting question arises as to what particular tissue or tissues of the body accomplish this remarkable feat.

Abderhalden set himself the task of experimentally answering this question. In conjunction with Pernuchi, Hunter, and Rona, he prepared extracts and juices of various organs, using Buchner's method of grinding up with sand and expressing the juices under a pressure of one hundred to three hundred atmospheres, by which method the cell enzymes are obtained. The tissues thus treated included the liver, the kidney, and the muscles of rabbits and dogs; lenses from the eyes of pigs; the brain of the calf; blood serum of ox, rabbit, and dog; and blood corpuscles of various types. Different types of polypeptids were used, to test the selective affinities of the various enzymes.

It was found that the juices of each and all of the tissues just named (as also juices of germinating wheat, germinating lupine, the mushroom, and various moulds) contain enzymes that hydrolyze one or another of the polypeptids; each juice, as a rule, acting on several different types of polypeptids. Juices of liver, kidney, and muscle hydrolyzed the simpler polypeptids. The plasma and serum of the blood both hydrolyzed complex types of polypeptids, which are known not to be attacked by trypsin, proving that the blood fluids did not receive their enzymes by absorption from the intestinal tract.

But, in any event, it was needless to look far afield for the origin of the enzymes in the blood fluids, inasmuch as the juices expressed from the red blood corpuscles proved capable of hydrolyzing the most complex polypeptids.

The leucocytes of a horse, on the other hand, failed to hydrolyze a polypeptid which the red blood corpuscles of the horse, and also the blood platelets, hydrolyzed actively. Blood plate-

lets, there is reason to believe, are only extruded contents of red corpuscles.

It may fairly be concluded, then, that the hydrolyzing of polypeptids that find their way into the blood stream may be accomplished by enzymes secreted by various organs and tissues, including the muscles; that the red blood corpuscles are very active agents in this capacity, notably, perhaps, with regard to the most complex polypeptids; and that it does not fall within the range of the activities of the leucocyte to deal with these comparatively simple nitrogen compounds. The leucocyte, like the organs that produce the digestive ferment of the intestine, acts on the full-sized protein molecule, and begins its cleavage. But in the light of the new evidence, it may somewhat be doubted whether the leucocyte is able to carry on this cleavage to its final conclusion. It is at least possible that the protein molecules, multiplied by cleavage, acquired an osmotic pressure that causes the disruption of the leucocyte when the polypeptid stage of hydrolysis has been reached. If such is the case, the autolyzed leucocyte would discharge its contents in the midst of myriads of red blood corpuscles capable of taking up the work of hydrolysis where the leucocyte left it, and completing the cleavage of polypeptids into amino-acids.

According to the hypothesis already expounded, it would be only comparatively small quantities of foreign protein that would thus come under the auspices of the leucocyte; but it is not unlikely that considerable quantities of polypeptids may find their way habitually into the blood stream; and it is to be recalled that the red corpuscles, marshaled in numbers not far from a thousand times as great as the number of leucocytes, should be able to deal with the polypeptids in almost any quantity.

It is even conceivable that all the protein foodstuffs are absorbed in this state (since the evidence for their change into amino-acids in the intestinal wall is not quite conclusive), and normally undergo their final stages of hydrolysis under influence of the erythrocytic enzymes; the tissues of the liver and brain and muscle standing guard meantime in the background, as it were, ready to attack (each within the limits of its capacity) any portions of polypeptids that escape the militant army of red corpuscles. The numbers and aggregate bulk of the red corpuscles suggest their possible capacity to accomplish such a task.

These experiments, then, enable us to form a more complete and more satisfying mental picture of the processes of digestion and assimilation than has ever hitherto been possible. We shall be able to fill out certain gaps in the picture as we proceed, ultimately presenting at least a suggestive scheme of the entire cycle of protein metabolism in the body.

New Experimental Evidence

The above exposition of the theory of proteolytic activities of the red corpuscles is reproduced precisely as it was presented in the original exposition of the Proteomorphic Theory in *American Medicine* of October, 1914. It will be obvious that the hitherto unsuspected function thus ascribed to the red corpuscles matches in importance, if its validity is demonstrated, the function of carrying oxygen to the tissues—each being absolutely essential to the life of the individual. The subject having such fundamental importance, then, it will be of interest to cite here a series of experiments made about two years later, which give strong support to the theory of erythrocytic polypeptid digestion.

The experiments in question have to do with the distribution of the residual nitrogen between the blood cells and the plasms, originally published in the *Biochemische Zeitschrift,* as reported in *Physiological Abstracts* (published by the Physiological Society of Great Britain and Ireland with the co-operation of the American Physiological Society) in the tissue of October, 1916. The experimenter was Dr. Ivar Bang. The abstract is as follows:

"The residual and urea nitrogen in the blood and plasma were determined in well-nourished rabbits before and after a seven-day fast during which no water was given. The amino-acid fraction was represented by the difference between the residual and urea nitrogen. In accordance with the findings of earlier experiments, an increase in residual nitrogen occurred after the fast which concerned the urea fraction only. Before the fast urea was equally distributed between the cells and the plasma, while the cells were richer than the plasma in amino-acid; these relations persisted after the fast.

"After the introduction of a solution containing two to three grams of glycine into the bowel, there was an increase in the residual nitrogen of the blood, which affected the amino-acid fraction almost exclusively. The increase was confined to the plasma, and hence the amino-acid content of the blood cells is probably formed in the cells themselves."

It will be observed that "blood cells" as a whole are here referred to, with no specific reference to the red cells. But the fact that the latter are about one thousand times as numerous as the leucocytes, constituting the main bulk of the formed matter of blood, makes it highly probable that the amino-acids in question were contained very largely at any rate in the eryphrocytes.

Such experimental proof of the completion of protein hydrolysis in the corpuscles is interesting from a theoretical standpoint,

but doubly so from the practical standpoint of the physician administering proteins therapeutically. There remains little doubt that the red corpuscles are an essential part of the mechanism through which intruding proteins are ultimately reduced to innocuous amino-acids.

It becomes necessary, then, to watch the red corpuscles no less than the white ones as an aid to the interpretation of the patient's progress. Not merely their numbers, but their qualitative conditions should be considered—the presence of normoblasts, megaloblasts, poikailocytes, crenated and friable cells, and the like should be closely observed, as giving clues to the regulation of dosage, a change of frequency of administration, or a modification of the type of proteal employed.

The fact that the proteals produce rapid and significant modifications in the number and character of the red cells has been too frequently observed to be matter of doubt.

The subject has obvious importance, from the standpoint of the practical physician, as will appear when we take up the question of the therapeutic protein response in later chapters.

The Red Corpuscle as Master Immunizer

But where, it will naturally be asked, is the point of contact between this scheme of polypeptid digestion and the development of antitoxins?

The answer is this: The bacterial toxins that evoke the responsive antitoxins are products of protoplasmic activities; and they are known to be comparatively simple in chemical composition, their molecules being in all probability of the same order of complexity as the molecules of polypeptids. It is a fair presumption that the bodily enzymes proved to act on the polypeptids are the ones that act also on these allied bacterial toxins.

If the inference is justified, the sources of the antitoxins are clearly revealed: They are the cells of the entire body, each type having a selective action of its own; and, in all probability, the red blood corpuscles being the ones that have the most general and the most comprehensive activities in this connection.

Now it is obvious that so bold an assumption as this requires all the support that can be found for it in analogical reasoning. Fortunately there are several lines of such reasoning that supply confirmatory evidence.

Thus, bearing in mind the nitrogenous character of the waste products of protoplasmic action in the animal organism (for example urea, with the formula CH_4N_2), we are justified in assuming that the toxic principles given out by the virulent bacteria are not altogether dissimilar nitrogenous compounds. This

assumption is strongly supported by the observed similarity of action of these toxins and sundry narcotic drugs of the familiar alkaloids. And these alkaloids have known chemical formulæ that at once reveal their chemical relationship with the polypeptids.

Morphine, for example, is $C_{17}H_{19}NO_3$; strychnine is $C_{21}H_{22}N_2O_2$; and glycyl-glycine, the simplest of the polypeptids has the formula $C_8H_{16}N_4O_6$. If we knew how to combine the amino-acid called valine ($C_5H_{11}NO_2$) with the amino-acid called leucine ($C_6H_{13}NO_2$), we should have a molecule with the composition $C_{11}H_{24}N_2O_4$, in still closer simulation of the strychnine molecule. The combination of two molecules of the amino-acid, glycine with one of leucine, which has been effected, gives the formula $C_{17}H_{33}N_3O_7$.

Of course, we can by no means assume that because the combinations of atoms in a given pair of molecules are similar the gross physiological effects of these molecules on the organism will be identical or even comparable. To disprove any such hypothesis, nothing more would be necessary than to consider the chemical composition of certain other alkaloids, for example quinine, which, with its formula $C_{20}H_{24}N_2O_2$ seems to have close touch with strychnine; yet which, as every tyro in medicine knows, is very fundamentally different in its physiological action.

It should be understood, however, that in the modern view a drug acts on only those tissues with which it can enter into chemical union; and that the markedly different physiological actions of drugs depends upon the affinity for them shown by this or that type of cell in the tissues of the body. Quinine and strychnine appear to us radically different drugs, because their effects on the human system are so conspicuously diverse; yet their chemical composition proves their close similarity; and a reasonable explanation of the difference in their effect is given if we assume that the precise combination of "side-chains" in the strychnine molecule chances to fit in with the scheme of the molecules making up the substance of the central tissue of the brain; whereas the side-chains of the quinine will link it with other tissues that are in themselves no less profoundly affected than are the brain tissues by strychnine; but which are not so vitally and intimately associated with the life-processes of the organism as a whole.

It is in the fact that most alkaloids, in common with toxins, find their affinities in the cells of brain and spinal cord that the seeming toxicity of these substances lies. Many a "harmless" compound may affect muscle cells, let us say, far more profoundly than the brain cells are affected by morphine or strychnine, yet have no "toxic" effect, because the muscles do not

contain the centers of cardiac and respiratory control, as do the nervous centers.

Considered in this broad way, there is ample justification for the belief that the physiological activities of all drugs are intimately linked with their chemical composition; and that, in the sense just interpreted, drugs of closely similar chemical composition have strictly analogous effects.

But everything depends upon the particular tissue cell which chances to have affinity for any given drug; and the experiments of Abderhalden as already cited, showing the elective affinities of different tissues for polypeptids, may be considered as laboratory interpretations of familiar facts of clinical medicine. The fact that many alkaloids and such poisons as that of *B. tetanus*, and, indeed most of the bacterial toxins, give evidence of affecting the brain, dove-tails, at least presumptively, with the highly interesting experiments that show that two of the most complex of the polypeptids were hydrolyzed by the juices expressed from the brain cells of a calf.

It may be added that in the case of two less complex types of polypeptids, the juices of the calf-brain failed to act; and conceivably it is not stretching analogies too far if we observe that the alkaloids which are known to have a pronounced cerebral effect are considerably more complex, particularly as regards their carbon and hydrogen atoms, than the simpler (di-amino) polypeptids; and if we associate relative complexity of molecular structure in a drug with affinity for the cerebral tissue, in itself presumably the most complex of organic bodies.

Such a conception must be held with great reserve, however, in view of the extraordinary toxicity of the simple combinations CS_2, carbon bisulphide, and HNC, prussic acid, and of the conflicting evidence elicited by observation that, whereas nitriles of the fatty series, from acetonitrile to isovaleronitrile, increase in toxicity with growing molecular weight, substances of an allied series, starting with cyanacetic methyl ester, $C_4H_5HO_2$, become less toxic (according to Berthe and Ferre) with increased complexity, losing toxicity altogether when two groups of $C_2H_5O_2$ are inserted. A clue will perhaps be found in the study of the valencies of the nitrogen atom, which, as is familiarly known, is either trivalent or quinquevalent.

Specific Affinities and Antagonisms

Closely in keeping with these rather abstruse theoretical considerations are the familiar and very practical experiments of Pasteur through which the anti-rabic virus was developed. Here, as is well known, the material used for making the protective

inoculation is found in the spinal cord of a rabbit that has been successively inoculated with the virus of rabies.

Equally suggestive in their way were the experiments of Wassermann, who mixed tetanus toxin with the brain substance of a susceptible guinea pig and found that the mixture was no longer toxic for other guinea pigs. This seemed to show a special affinity between the brain substance and the toxin, inasmuch as emulsions of other organs of the guinea pig when brought in contact with the tetanus toxin exerted no such effect. "It would appear from this experiment," says Nuttall, "that a toxin may have a special affinity for special tissue cells, and this appears to explain the neuro-toxic character of the symptoms which are observed in tetanus."

It would be better, perhaps, to say that certain cells have an elective affinity for the toxin, rather than to make the converse statement; best of all to think of the attractions as mutual. In chemical terminology some cells have side-chain groups of molecules for which the molecules of the toxin can readily be substituted; or with which they may be combined through a new arrangement of the atoms. What determines these affinities we shall not know until we are better informed as to the ultimate nature of chemical valences in general; but for the present purposes it suffices to note the seeming demonstration that such elective affinities exist, and that they are exercised by various tissue cells of the body in connection with an endless variety of nitrogen compounds.

Another very striking illustration of such elective affinities, in this case involving the muscle cells of the unstriped muscles, is furnished by the amino-acid-like product, known as adrenalin.

The origin of this product in the supra-renal glands, and its extraordinary effect in constricting arterioles, are familiar to the profession. But it may not be so generally known that adrenalin differs by only two hydrogen atoms in chemical composition from one of the familiar amino-acids named tyrosine. Such, however, is the fact, the formula of tyrosine being $C_9N_{11}NO_3$, and that of adrenalin $C_9H_{13}NO_3$. That adrenalin exercises its contractile function by directly influencing the muscle fibers of the arterioles is shown by the continuance of its characteristic action when applied locally after severance of the nerves leading to the tissue under treatment. Let it be observed, too, that it is the cells of the unstriped muscles alone that seize on the adrenalin molecule; the cells of other muscles seeming to let it pass unnoticed.

When we add that adrenalin exists normally in the blood only in the proportion of one part in a million, yet that its presence

in this infinitesimal quantity seems necessary to the very life of the organism, light is thrown from yet another direction on the intricate co-ordinations of the animal machine as effected with the aid of the nitrogen-bearing molecule.

Here is a substance which, were we able to remove but two of its hydrogen atoms, would become merely a commonplace member of the group of amino-acids, ready to be taken up by this, that, or the other tissues of the body, as a component part of its protein; and yet, in virtue of the presence of those two supernumerary hydrogen atoms, it gains special affinity for cells of a particular type, and causes those cells, in recombining their structural materials, to undergo a destructive metabolism of an almost explosive type which finds tangible expression in a muscular contraction.

Could we look into the structure of the muscle cells during this time of its explosive activity, with vision more ultra-microscopic than is afforded by any instrument yet devised, we should see that the cell, in readjusting its molecules, has some left-over materials, like the shavings and sawdust of a carpenter, that are not needed in the new combinations; and that these left-over products are excreted into the surrounding fluid medium. And what is true of the muscle cell under these circumstances is equally true of every other muscle cell whenever it contracts from whatever cause, and of the cells of every other bodily tissue when they undergo characteristic activities. Changes in the molecular structure of the cell—incident to or underlying all activity—are affected only at the expense of potential energy, and with actual gain or loss of physical material. Destructive metamorphoses, which attend the active functioning of all tissues, are attended by a loss of substance. And it is almost axiomatic to say that the precise character of the substance given out as a waste product or a by-product must be dependent on the character of the substance available to replace it. On occasion there comes to hand, let us say, a group of atoms that is admirably suited to fit into the structure of the molecule of the cell, provided that another group similar in character, but, on the whole, somewhat less satisfactory is excluded. So the substitution is made, and the discarded group of atoms flows away in the blood stream.

It is obvious that groups of atoms that can thus be substituted one for the other may bear to each other a certain complementary relation. It is one way of expressing this relation to say that the intruding molecule is an antigen, and that the extruded one is an antibody. In view of the mutual relations of these structures, it does not seem strange that members of the two clans, when they chance to meet in the blood stream, can enter into

mutual combinations. Two groups of atoms each of which can unite with a third group may very well unite with each other. But when the antigen has thus combined with an antibody, it no longer has free valences, and so it cannot combine with the cell that it formerly would have entered. In the event that the particular antigen in question was the kind of plotoplasmic product that we call a toxin, we may well enough call the antibody an antitoxin; and we may speak of the union of the two as neutralizing the poison and rendering it harmless. But this, of course, applies only to exceptional instances in which the antigen had properties that made its presence objectionable in the cell with which it has affinity. Most antigens that would ordinarily be found in the body have not such harmful properties, and their antibodies, although acting in the same way, would not serve the same purpose.

But at the moment, of course, I have specifically in mind the antigens that are toxic; and their specific antibodies are the antitoxins. And the purport of the present phase of the discussion is, it will be recalled, to make it seem plausible, on various analogical grounds, that each and every living cell of the body must on occasion take to itself what we may call antigens, and give out what we may call antibodies; and that the particular tissues that can produce antibodies in response to any given toxins are precisely those tissues that are receptive to the invasion of that toxin.

If the toxin be one for which the brain tissues have pre-eminent affinity, the antitoxin produced will come from the brain cells. If the toxin be one attacking the liver, the liver cells will furnish the antitoxin.

However specialized any cell may be to perform pre-eminently a particular function through division of labor in the entire body every cell must retain the primitive capacity to take in nourishment and give out excrementitious products, else it obviously could not maintain existence. And it is conceived that the production of an antitoxin in response to a toxin that the cell can absorb is merely a special manifestation of this primal and fundamental function.

The bacterial toxins are, according to the present hypothesis, relatively simple nitrogen compounds of a type suitable for combination with various of the body cells—not distantly related to the amino-acids; the production of complementary bodies or antitoxins by these body cells, under these conditions, may be said to be a commonplace of physiological activity—though sharing, of course, in the inscrutability that attaches to all chemical processes.

Loss and Gain Through the Division of Labor

But the reader who would clearly apprehend the bearings of the theory of immunity thus exposited must on no account fail to note the exact terms of this definition just given. The antitoxins, in this view, are produced by various and sundry of the body-cells, because these antibodies are evoked in response to the coming of toxins that are relatively simple nitrogenous compounds. When, however, the antigen that comes is not a by-product of protoplasmic activity, but the protoplasm itself as evidenced in the body of a bacterium or in molecules of unbroken protein in any form, the case is quite altered, because the body-cells in general are not adapted to absorb such materials. Their location in the body, shielded by encompassing walls of skin and mucous membrane, puts them out of contact with such crude raw materials, the transformation of which has been turned over to an especially adapted apparatus known as the digestive system.

Each cell must retain the capacity to take food; but it may have lost the capacity to imbibe this food in a crude or undigested form.

Such is indeed the condition of the specialized cells of the brain and muscles and of the parenteral organs in general. The penalty of their specialization is that each of them, while gaining in one feature, has lost in various others. The single speck of protoplasm that constituted the entire structure of the primordial protozoal ancestor was at once stomach and muscular system and circulatory apparatus and brain. But in the developed organism each individual cell retains only the faint reminiscence of each type of function except the one for which it has been especially developed; and this one it can carry out in exaggerated fashion. The particular cells that have made themselves masters of that department of the work which has to do with the ingestion of food and the splitting up of proteins is called the digestive apparatus; and its work is supplemented, we have found reason to believe, by the leucocytes and erythrocytes.

But when, as occasionally happens through inadvertence, a considerable quantity of protein in the unbroken form makes its way into the circulation and comes thus (unmodified) in contact with the body-cells in general, it is as useless to these cells as if it were composed of utterly unassimilable materials.

The proof of this is that proteins thus introduced in quantity are excreted unchanged through the kidneys. The leucocytes and erythrocytes, to be sure, deal with part of this foreign protein; but their capacity is limited, and beyond that nothing remains but to eliminate the foreign substance as rapidly as possible. In

case this cannot be accomplished, the protein which might, under other conditions, be invaluable as food for the tissues becomes a menace through a mechanical clogging of the spaces about the cells, and perhaps through the accumulation of partially metamorphosed product as the result of the activity of the leucocyte. Antibodies quite different from antitoxins will be developed by the leucocytes; but, of course, these can avail only if the foreign proteins come in relatively limited quantity.

Making an anticipatory therapeutic application, it is clear that the ideal to be aimed at when proteins are introduced hypodermically (as in Proteal therapy), is to give the dose that will evoke a maximum corpuscular response with a minimum introduction of foreign proteins that must themselves be proteolyzed. Whether this may best be accomplished by using a single foreign protein or by combining a number of such proteins is an important practical question that will be discussed later in this volume.

So much by way of recapitulation, and to make clear the distinction that I conceive to exist between the sources and the character of the antibodies as evoked by antigens that on one hand are protein bodies and on the other are the metamorphosed products of protoplasmic activity—so-called toxins.

The Coalition Between Red Corpuscles and White

Reverting now to the latter, in continuance of the theme, it remains only to point out that, whereas it is conceived that all the cells of all the tissues of the body have capacity for the production of antitoxins in response to small moleculed toxins, it would appear that there is one type of cell that is pre-eminently adapted, by virtue of its location in the organism, to absorb these toxins and render them innocuous; at the same time, of course, giving out the residual products which we term antitoxins. The cells in question are the red corpuscles of the blood.

A very prominent function of these cells, according to the present thesis, is thus to shield the body-cells in general against the attacks of the numerous toxins that necessarily, under existing conditions, find their way more or less continuously into the blood stream. In particular, to shield the brain cells, because they take (in Abderhalden's experiments) the same type of complex nitrogen compounds that have affinity for the cerebral tissues. Ordinarily the red corpuscles come in contact with them first, and thus the brain is protected.

As justification for the conclusion, we have the entire line of analogical reasoning just presented, supported specifically by the experiments of Abderhalden, which showed, it will be recalled, that the red blood corpuscles manifested exceptional activity in

the proteolysis of those polypeptids which I have all along likened to the toxins.

Of course, the specific antitoxins developed by the red blood corpuscles would, in the nature of things, be liberated into the blood plasma. But there would doubtless be a good many compounds formed that could not advantageously be thus disposed of; and possibly it is to meet the complications thus introduced that the body has developed the custom of destroying vast quantities of the red blood corpuscles constantly in the liver, where the refuse matter they contain may be promptly eliminated in the form of bile. It may be doubted whether any other hypothesis hitherto presented more plausibly accounts for the constant destruction of red blood corpuscles (estimated to represent about three per cent. of the entire corpuscular supply daily), which, at first blush, seems to set at defiance the usual bodily custom of conserving materials.

In this view, then, the red blood corpuscles have an immunizing function strictly complementary to that of the white blood corpuscles, and no less important. One legion of cells co-operates with the other, each having its own special field. The white corpuscle deals with all formed bodies and full-sized protein molecules of foreign type that make their way into the blood stream. The red blood corpuscle deals with the later cleavage products of protoplasmic activity. In carrying out their respective tasks, the leucocyte supplements the work of the ferments of the digestive tract; the red corpuscle supplements the work of the leucocyte and relieves the ultimate tissues in considerable measure of the task of protecting themselves against small-moleculed nitrogenous end products that might prove harmful.

Interpreting the work in the words of the bacteriologist and pathologist, we may say that the leucocyte, in the pursuance of its general scavengering function, produces "complement" that is a digestive ferment somewhat of the order of trypsin; and "antibodies" of the types known as bactericides, bacteriolysins, opsonins, and precipitins; also antitoxins to neutralize the offensive or defensive toxins put forth by the living bacterium. Meantime the red blood corpuscles, aided and supported on occasion by various and sundry of the specialized tissues—liver, kidney, muscle, brain—produce complements of a different order from those produced by the leucocyte, capable of dealing only with partially hydrolyzed protein products; and produce also specific antitoxins that chemically neutralize bacterial toxins and in particular the final by-products of bacterial decompounding, but do not attack the bacteria themselves. It is not unlikely that hemolysis also falls within the scope of the erythrocytic activities.

If the implications of the theory are clearly grasped, it will be obvious that, according to the present view, there is no fundamental distinction between the various "complements" and "antibodies" thus defined. The word "complement" as commonly used merely serves to define such members of an endless series of ferments as are relatively susceptible to the influence of high temperatures. The line of demarcation thus established has obvious practical value; but we should not be led thereby to imagine a duality of action which in all probability does not exist in fact.

What we term "complement" in any given case is the ferment or combination of ferments regularly developed in quantity by the cell in question to meet the more or less habitual needs incident to the ingestion of proteins of its environment. What we term an "antibody" in any given case is one of a series of ferments developed in response to a specific impulse given by an individual type of protein or protein product. The trypsin of the leucocyte would stand at one end of that scale; the antitoxins of the red corpuscle at the other; but there would be intermediate forms to cover all the field between the two, each enzyme doubtless overlapping more or less with its neighbors.

That the general ferments or complements should be themolabile and the antibodies relatively thermostable may conceivably be due to the greater complexity of the former, consistent with their more generalized function. But that there is any radical and fundamental distinction in the nature of the two types of structures seems theoretically improbable.

The demonstration or refutation of the validity of this assumption, however, is a matter for the chemistry of the future, with its extended knowledge of the nature of enzymes in general.

CHAPTER II

THE PROTEOLYTIC MECHANISM IN OPERATION.

Such, then, is the immunizing mechanism of the body as I conceive it: (1) a system of lymphoid tissues, comprising lymphatics, bone marrow, and spleen, and sending into the field legions of leucocytes and still greater legions of red corpuscles to support them; (2) body-cells of many types standing in the background, each equipped only for individual defense; and (3) the liver and kidneys as the chief excretory organs of the by-products of the conflict. This is the system which guards the body from within, as skin and mucous membrane guard it from without, against the intrusion of foreign proteins of every type, and against the products of proteid activity.

Some further details as to manner of working of this important mechanism may perhaps be presented to best advantage if we make inquiry as to precisely what takes place on the various occasions when the efficacy of the defensive mechanism is put to an exceptional and decisive test.

Let us assume a case in which a few molecules of unbroken protoplasm have found their way through the intestinal wall—evading the pepsin and trypsin and erepsin of the digestive tract—and enter the blood stream. This is not a strictly normal occurrence, to be sure, but it must be a very common one, under slightly maladjusted conditions of digestion, as the experiments already cited show. In these experiments the proteins proved thus to enter the circulation unbroken, including those of egg albumen, blood serum, and milk. So we may fairly assume that any of the ordinary food proteins may on rather frequent occasions find their way in small quantities into the blood stream. We have now to inquire what happens to them there.

The inquiry has practical interest for the clinicism no less than for the physiologist, because it is obvious that it applies equally to the bodily activities responsive to the therapeutic introduction of a foreign protein, through the hypodermic injection of a serum or vaccine or proteal. There are very important quantitative differences, however, evidenced in the varying degrees of toxicity, as interpreted by the clinicism.

Let us first consider the case in which the introducing protein comes through the intestinal wall, through partial failure of the normal digestive enzymes. Then, according to assumption, the protein is a mere fragment of a normal food stuff; but it is a

disturbing element in its present location. According to the theory here presented, what happens to it is this: the leucocytes having had to deal with this particular type of protoplasm many times before have already secreted into the blood serum an enzyme (allied to trypsin) that is capable of attacking the protein and accomplishing the early stages of its proteolysis. This process will be facilitated if the molecules of foreign protoplasm chances to be engulfed in the body of a leucocyte. But in any event the leucocytic enzymes will hydrolyze the protein to the peptone stage; conceivably to the stage of polypeptids.

At this stage the partially hydrolyzed foreign protein is turned over to the red blood corpuscles. To them these particular polypeptids are familiar materials, since they have dealt with their like often enough before, and the particular department of their enzymes-making apparatus that will deal with these specific polypeptids is in good working order; indeed, the enzymic products are already in the blood stream. So the further hydrolysis of the intruding matter is rapidly carried forward; with the result that presently the main bulk of the material has been transformed into amino-acids—thus supplying normal material for the uses of the cells that are to build up the specific body proteins.

We must suppose, however, that there is a small residual matter, of doubtful constitution, which has not been thus hydrolyzed; for the complete hydrolyzation of a protein through the agency of enzymes has not been accomplished in the laboratory, and we have no reason to suppose that it is accomplished in the body. It requires from two to five hours of digestion in strong hydrochloric acid to hydrolyze protein completely *in vitro;* the organism has no enzymes of corresponding power.

But, according to hypothesis, the residual molecules, whatever their exact nature (uric acid, urea, bilurubin), have been largely or perhaps exclusively developed in the bodies of the red corpuscles; with the result that the corpuscles themselves are more or less damaged. The residual molecules, that is to say, are poisonous to protoplasm. The red corpuscle in retaining or absorbing them is thus injuring itself, but protecting the body-cells that would otherwise absorb the poison.

But whereas such an injury to the body-cells would be highly detrimental to the entire organism, the injury to the red blood corpuscle is not necessarily a matter of consequence. The corpuscle bearing its poison is whirled on in the blood stream until it comes to the liver, and there destroyed, its noxious molecules being discharged, with countless others of similar origin, into the bile duct.

It would be interesting to inquire as to just what is the char-

acter of the physiological action that leads to the destruction of the red corpuscle, but this would carry us too far afield.

Conceivably osmotic pressure alone may suffice; the substance of the hemoglobin being in part decompounded by the imbibed foreign enzymes, and its osmotic pressure thus enhanced. Rupture would then be likely to take place in the liver, because that organ serves as a great lagoon in which blood from the portal vein becomes relatively static, and reduced in pressure. Somewhat similar conditions in this regard obtain, it may be added, in the spleen; and it is perhaps significant that many physiologists believe that this organ also is the seat of erythrocytolysis.

In any event, through osmotic or chemical action disruption does occur, and the unassimilable remnant of the foreign proteid is thus extruded into the intestine, whence it originally came; the general protein content of the red corpuscle (transformed now through partial disruption into globulin and albumin) being liberated to contribute to the regular protein contents of the blood serum.

It requires but the most casual study of corpuscles in the Toisson solution in the counting chamber to suggest the widely differing conditions of osmotic pressure among the corpuscles of a drop of blood, and the diversified conditions that obtain in association with various toxæmias. In freshly drawn supposedly normal blood all the erythrocytes will appear smooth in contour, the cell-membrane seemingly taut. But in the course of half an hour or so the appearance of most of the corpuscles may be utterly changed. They become shriveled, and assume the appearance of diminutive sea urchins. Modifications of size and contour continue, presumably, until the contents of the cell become isotonic with the saline medium.

It is my belief that valuable inferences may be drawn as to the physiological and pathological activities of the corpuscles, in individual cases, from study of the variable time and character of modification undergone by the corpuscles in thus reaching a state of osmotic equilibrium.

For example, cells that shrivel in a medium of moderate hypertonicity may be assumed to have a large-moleculed content. And this gives presumptive evidence that the functions of completing hydrolysis of absorbed peptones or polypeptids is being performed sluggishly or inadequately. In such a case compensation may for a time be effected by increase of red corpuscles, and we are confronted with the clinical paradox of a virtual anæmia in which the number of erythrocytes is perhaps five and a half or six million.

If in such a case the white corpuscles appear fairly normal in number, quality, and differential count, it may be inferred that

the patient suffers from protein end product absorption—a common and characteristic form of intestinal toxæmia.

In a typical case of this description recently under my observation, the patient is a youth of eighteen, with no pronounced clinical symptoms other than habitual constipation and susceptibility to infection ("catches cold" readily; has occasional crops of boils). Pulse 68; blood pressure, 120-80; hæmoglobin, 85-90. The white corpuscles numbered 6,400, and on the smear appeared normal purple and showed no tendency to clump. Red corpuscles, 5,608,000, largely checkered and vacuolated when fresh in (diluted) Toisson solution; platelets fairly numerous. After three hours ninety per cent. shriveled, spiny, more or less distorted (a condition I am accustomed to refer to in my laboratory notes as the "sea urchin" effect); so small as to show pronounced Brownian movement.

Closely similar blood conditions are often found in patients suffering from chronic arthritis. This is not the place, however, to discuss in further detail the pathological and clinical bearings of the implied disturbances of the erythrocytic function of ultimate protein hydrolysis. That observation of the corpuscles in this connection have practical bearing on problems of disturbed digestion and assimilation clinically spoken of as autointoxication and intestinal toxæmia, will be obvious. Full discussion of the phenomena in question, with particular reference to acidosis and the rheumatoid condition, will be given in a subsequent chapter.

The Phenomena of Anaphylaxis

But suppose now that the protein that enters the blood stream, instead of being the product of a familiar foodstuff is a protein of an unusual type—that is to say, one that the organism does not habitually ingest. Or suppose that the protein, although of a familiar type, is introduced in rather large quantities. In either case complications arise; and these complications are precisely similar in character in the two cases, being due in each case to the inadequacy of the protective equipment, as will appear in a moment.

Illustrative cases in point are the laboratory experiments in which a foreign protein is injected into the system of a rabbit or guinea pig; and, in case of a human subject, those instances in which proteids are ingested in great quantity and fail of normal complete digestion.

In either case the phenomena may result that have become more or less familiar under the name of anaphylaxis. It is a condition of toxicity in which the symptoms clearly indicate in-

volvement of the brain—or, at all events, of the central nervous system.

In the laboratory experiments this condition of so-called anaphylactic shock may occur after a single inoculation with a large dose of a foreign proteid; but in that case it is somewhat delayed.

The condition is usually induced by following a small initial dose of protein (which has no apparent effect) with a larger one at an interval of a week or ten days. A strictly comparable condition is sometimes produced in the human subject through the use of antitoxic serums, anaphylaxis being due not to the antitoxin itself, but to the foreign blood serums (usually that of the horse) in which it is suspended. In the case of the animal in the laboratory, the condition is often fatal, sometimes very rapidly so. In the case of the human subject, it may constitute a serious "serum disease."

My personal observation of the phenomena of anaphylaxis in the human subject has been chiefly associated with the therapeutic administration of sheep serum (antithyroid) and various vegetable proteins (proteals). A mild anaphylactic reaction may manifest itself locally, a few hours after the hypodermic injection is given, by a condition of erythema at the point of injection, involving only a small locus, or in some cases extending to the entire arm. There may be marked ecchymosis of the tissues, with attendant swelling lasting for twenty-four or forty-eight hours.

Whether or not there is pronounced local reaction, there may be a general reaction two or three hours after the protein is injected, manifested by rise in temperature, accelerated pulse, feeling of malaise, and a more or less pronounced chill. These symptoms disappear presently, without calling for treatment.

Very different are the manifestations of acute anaphylactic shock that may occur when a patient who for some time has been under protein treatment receives by accident a full dose of the protein into a vein. The anaphylactic reaction supervenes in the course of fifteen or twenty seconds. The patient's face flushes violently, more or less severe pains are located in the head and back, and the pronounced dyspnœa simulates an acute attack of asthma. In extreme cases the patient may lose consciousness. The violent symptoms usually subside rather quickly, although the backache may persist for fifteen or twenty minutes. Aromatic spirits of ammonia may be administered, and the backache may be controlled by a few whiffs of chloroform. Caffeine may be given to stimulate the heart. But all these measures are more or less of the nature of placeboid palliatives. The patient rallies quickly even without treatment, and, except perhaps for the persistence of a frontal headache, soon feels as well as

ever. The experience, nevertheless, is an unpleasant one for both patient and physician.

But fortunately an anaphylactic shock of this character from the administration of a protein in therapeutic doses is exceedingly rare. I have personally witnessed it only a few times in the course of an experience covering the administration of thousands of doses of proteins. Moreover, it would appear that the vegetable proteins, when partially hydrolyzed, as in the preparations of the Proteals now made in my laboratory, do not produce anaphylactic reactions of this character. A possible explanation of this gratifying modification will be attempted in another connection. For the moment we are concerned with the general theory of the anaphylactic response.

The current interpretation of this condition is that the first injection of the foreign protein has "sensitized" the tissues, so that when the second injection occurs there is a sudden and morbid reaction. Vaughan explains the condition far more plausibly as not due to an increased sensitiveness of the tissues, but to the presence of enzymes of the antibody order induced by the first inoculation. He suggests that this ferment is put forth in sufficient quantities not merely to neutralize the protein that called it forth, but to saturate the blood more or less; so that when the second dose of protein appears its molecules are immediately broken up in such a way that the poison group is released and enabled to act upon the tissues toxically.

But this suggestion involves an obvious and fundamental difficulty; it assumes that the antibody put forth in response to a foreign protein will become a menace instead of protection—which precisely reverses the prevalent and seemingly correct interpretation of the character of antibodies.

According to the view of the present writer, the *rationale* of anaphylaxis is something quite different from this. In my view, there is no question of "sensitizing" the tissues to a foreign protein; inasmuch as they are inherently sensitive to all proteins, foreign or otherwise, at the proper stage of disintegration. Nor can I conceive that the system has developed the incongruous habit of putting forth, in response to a protein invasion, antibodies that will necessarily menace the system itself in the event that the invasion is repeated. Such a phenomenon would seemingly be an exact contradiction of the established customs of the organism.

Yet how are we to explain the anomalous fact that the organism was seemingly unaffected by the first dose, and yet was severely poisoned by the second one, administered after an interval of several days?

In my original exposition of the subject, I suggested that the

Proteomorphic theory supplies a clear and definite answer, conditioned on the activities of the white and red blood corpuscles in the regular processes of assimilation, as already outlined. It assumes that the white blood corpuscle began the proteolysis of the first dose of foreign protein, and that the red blood corpuscle completed it, quite as before; but that the specific enzymes of the red corpuscle adapted for dealing with that particular protein were present in very limited quantities in the blood, and susceptible of being reformed but slowly by the corpuscle, precisely because the organism was little subject to that particular invasion. Meantime, however, the more generalized enzymes of the leucocyte, known to be largely non-specific in action, were able to begin hydrolysis of the second dose of foreign protein when it appeared, reducing it to the polypeptid stage at which the red corpuscle should take it in hand. But these corpuscles, exhausted at the moment of the specific ferment (from dealing with the first dose) are, for the time being, helpless. They will gradually replace the lost enzymes, of course; but as yet they have not had time to do so, at least in adequate quantity, so the foreign polypeptids pass on to the tissues, and some of them are seized on by the brain cells with disastrous results.

The difficulty arises, it will appear, from the fact that the enzyme of the white corpuscle, which begins hydrolysis, is able to attack a great variety of proteins; whereas the enzymes to complete the hydrolysis of the resulting polypeptids must be made, in the case of any specific protein, in a particular department of the red corpuscles' laboratory.

To meet this necessity, the red corpuscle has developed a very elaborate type of protein, each molecule of its hemoglobin being composed of several thousand atoms; and under ordinary circumstances it is able to manage all the diverse materials that are turned over to it by the leucocyte.

But the circumstances under which anaphylaxis occurs are not ordinary. It is only a protein of unusual type, or a protein that comes in large quantities repeatedly, that can induce the condition, through disarranging the harmonious working of the proteolytic apparatus; except, indeed, that a single large dose of a foreign protein may, under exceptional conditions, be retained in the system for a considerable period (instead of being excreted rather promptly through the kidneys as is usual), in which case, obviously, there may be opportunity for the white corpuscle to begin proteolysis of larger quantities than the red corpuscles can handle.

In the case of the human subject, as just suggested, anaphylaxis may be due to the faulty digestion of the ordinary food proteids, under conditions that lead to the absorption of an excep-

tional quantity of unbroken protein. It may also result from the ingestion of an unusual type of protein, notably, of course of a type difficult of digestion. In general, we might expect that anaphylaxis from food proteids would result with a frequency in direct ratio to the rarity with which different proteids are digested. It is confirmatory that anaphylaxis from eating shell-fish, lobster, and various fishes seems to be somewhat more usual than that resulting from the proteins of beef, mutton, or fowl. A severe case of anaphylaxis from eating flesh of the snapping-turtle has come within the observation of the writer. Yet for most people the flesh of the snapping-turtle is entirely wholesome—as well as exceedingly palatable.

It should be observed that there are doubtless idiosyncrasies of individual organisms with regard to parenteral proteolysis, just as there are with regard to digestion; and this accords with the familiar laboratory observation that not all animals of a species suffer to the same extent from anaphylaxis under the same conditions.

In the consultation room, also, marked differences are to be observed among different patients. Some patients are peculiarly sensitive to any protein; others are peculiarly resistant to all proteins. Yet others appear to be sensitive to one protein, but resistant to another. Such idiosyncrasies are, of course, quite to be expected. It does not appear, however, that inherent susceptibility to a particular protein is necessarily associated with susceptibility to severe anaphylactic shock from the sudden introduction of a large dose of protein into the system previously "sensitized." Such "sensitization," in the view here represented, consists in surcharging the blood with corpuscular enzymes capable of affecting rapid proteolysis of the proteins in question.

The anaphylactic shock is probably to be interpreted as a vasomotor phenomenon. The almost instantaneous onset leaves it scarcely open to question that the primary action is exercised upon the vaso-motor and cardiac centers in the brain.

The reason, presumably, why shock takes place when the protein is injected directly into the vein, and not when the injection is merely subcataneous or intramuscular, is that in the former case a relatively large amount of protein is brought instantly in contact with the brain centers; whereas in the latter case absorption is slow and there is ample opportunity for the red corpuscles to perform their regular functions of shielding the brain cells by themselves absorbing the partially hydrolyzed protein molecules.

The observed fact that the therapeutic administration of the proteoses does not tend to produce the same anaphylactic shock that is produced by the full-sized molecule of the same type (for

example, alfalfa seed protein) is difficult of explanation. The thought naturally suggests itself that the anaphylactic shock may be due to the action of the full-sized protein molecule on the brain cells, which is not entirely consistent with the explanations of anaphylaxis above suggested. It should be understood, however, that this explanation is at best only tentative. The phenomena of anaphylaxis are exceedingly puzzling and by no means fully understood. I wish frankly to state that no other hypothesis in connection with the general thesis of the Proteomorphic theory is presented with greater diffidence or should be held with greater reserve than that connected with anaphylaxis. The full and satisfactory explanation of the subject awaits a much more comprehensive and penetrating knowledge of the general relations of foreign proteins in the blood stream to the central nervous system than is at present available.

Nevertheless, it appears to me that, in view of what we have already seen of the relations of the red corpuscles to the process of ultimate protein hydrolysis, the further investigation of the phenomena of anaphylaxis should be conducted always with the newly discovered functions of the red corpuscles clearly in mind.

As corroborating the view just presented, according to which protein-product intoxication is due to the incapacitating of the red corpuscle; and at the same time in corroboration of the general view that the red corpuscle is the agent called upon to deal with the toxic products of protein generation, we may recall the clinical fact that when a tapeworm dies in the intestinal tract, and decomposes there, the absorption of its toxic products may induce the condition known as *bothriocephalus anemia*, a characteristic symptom of which is the very great and persistent reduction in the numbers of the red blood corpuscles.

The red cells absorb the toxin, and effect its removal through the liver; but, owing to the persistence of the supply, such numbers of the corpuscles are involved that their ranks are presently depleted, the cytogenic apparatus being unable to manufacture them at so abnormal a rate. The general symptoms of pernicious anemia, due to reduction of the oxygen- and food-carriers, follow as a matter of course; but all the symptoms clear up rapidly so soon as the dead worm is expelled from the bowel.

The Synthesis of Protein

Incidentally, it may be urged that the profound systemic disturbances that accompany a reduction in the number of red blood corpuscles in this case would never result were the chief function of these cells merely to carry oxygen, as is commonly conceived. Under ordinary conditions the systemic cells require but

a fraction of the oxygen that the red corpuscles can carry, as proved by the fact that protein metabolism is unchanged when the corpuscles are artificially reduced in number by thirty per cent.

The new physiological studies which suggest that air may be breathed over and over without detriment—that, in short, the "fresh air" fetich is founded on a misconception of the needs of the organism—is of peculiar interest in this connection.

In any event, it would not seem to have been necessary to build a cell of an intricate type of protein merely to carry oxygen. Nor is it clear why the substance of the red corpuscle should contain nucleo-protein were it merely an oxygen-carrier.

But there was need of a cell carrying a molecule of intricate structure, in which might be stored the potentialities of an infinite number of atomic recombinations having their tangible representation in the output of endless series of enzymes calculated to carry the hydrolysis of proteins to its ultimate stages; as also to prove antidotal to an unending series of toxic by-products of protein metabolism in the living or dead tissues of the numberless species of animals and plants and micro-organisms with which the environment teems.

In the evolutionary history of the race, these needs have increased *pari passu* with the increasing activities of the individual organism, and the correspondingly varied character of the environment contact. And so we find, as we come up the animal scale, that the red blood corpuscles constantly increase in relative number in the blood stream. In fishes the red corpuscles form about twenty per cent. of the total volume of the blood; in frogs about twenty-five per cent.; with mammals it rises to from forty to fifty per cent., and the proportion of red corpuscles to leucocytes rises in something like the same proportion.

The primitive and generalized leucocyte retains from first to last the same appearance and, as I believe, fulfills the same primitive functions. It is a wandering phagocyte in the vascular system of the sponge; it remains a wandering phagocyte in the vascular system of man.

In the primordial state the red cell was relatively large and nucleated as it still is in the embryonic state, and in certain reversional diseased conditions.

But in the developed condition the reproduction of the corpuscles devolves upon the mother cells in the red bone marrow so the corpuscle itself needs no nucleus—or perhaps we should rather say that it is all nucleus, since it contains nucleic acids. It is decreased in size, giving it relative increase of surface, that it may more effectively patrol its environment; and it is sent forth from the mother cells in such galaxies that, under normal

conditions, there are five million individuals in each cubic millimeter of the blood-plasm.

In some of the lower mammals the number is far larger—in the goat, for example, upward of ten million; in the sheep, upward of fourteen million. Goat and sheep are not inordinately active creatures. Their oxygen needs can scarcely be so great as those of birds, which are said to have only from one million to four million red corpuscles to the cubic millimeter. But the herbivorous animals ingest large quantities of protein-bearing foods, and it is probable that the proteolytic demands made upon their corpuscles are far greater than in case of animals whose diet includes a large proportion of carbonaceous and fatty foods.

But, regardless of relative numbers, the red corpuscles lead a precarious life. Millions on millions of these cells are annihilated every hour in the juggernaut of the liver. It has been estimated that the destruction amounts to three per cent. of the total number each day—say, 150,000 corpuscles to each cubic millimeter of blood, or an aggregate bulk of perhaps sixty grams in the entire body. To gain a clear conception of what this means, recall that, according to Atwater's estimate, a man of average size requires only 92 grams of protein daily to maintain the nitrogen balance. Chittenden makes the amount far less. Yet the ranks of the corpuscles thus perpetually depleted are no less perpetually replenished. To build the new cells requires a constant supply of materials capable of being elaborated into an intricate type of protein. To build each molecule of this protoplasm requires some thousands, in the aggregate, of atoms of carbon and hydrogen and oxygen and the elusive nitrogen; some hundreds of molecules of amino-acids, the materials directly utilized.

The total energy required in the building up of these intricate molecules in the bodies of uncountable myriads of red corpuscles hour after hour and year after year, throughout the life of the individual organisms, is colossal. Each red corpuscle is a proteid body, its substance composed in part of hemoglobin, the formula for which has been computed as $C_{758}H_{1203}N_{195}O_{218}S_3$. To suppose that the organism exhausts this material and wastes the energy essential to its compounding merely to produce a transporter of unmodified oxygen would require a reversal of all our conceptions of economy of management in the cellular body politic. Yet such is the current conception of physiologists in general.

But there has been experimental evidence at hand for many years that, if properly interpreted, would dispel this misconception. As long ago as 1872 Bauer, in Voit's laboratory, studied the results of bloodletting in the dog, and found that when from eighteen to twenty-seven per cent. of the total blood in the

dog's body was removed, there was increased proteid metabolism, but no change in the carbon dioxide elimination. Some years later Finkler, in Pflüger's laboratory, withdrew one-third of the total blood from a dog, thereby reducing the rapidity of blood-flow in the femoral artery by one-half, without producing any change in the quantity of oxygen absorbed or of carbon dioxide exhaled. More recently Hawk and Gies have confirmed the early experiments to the extent of showing that there is a higher proteid metabolism after bloodletting.

Such experiments are utterly disconcerting so long as we consider the red blood corpuscle only as a carrier of oxygen. Note the conditions: the blood is reduced in quantity even by a third, the corpuscles being, of course, reduced proportionately. Yet the absorption of oxygen and the giving out of carbon dioxide are unmodified; and, even more strange to relate—according to accepted physiological teaching—the rate of proteid metabolism is increased.

There is nothing in the least anomalous about these phenomena, however, if interpreted in the light of the Proteomorphic theory. In this view, the mother cells that produce the red corpuscles, together with those that produce the leucocytes, constitute the great protein-synthesizing mechanism of the body. Out of the amino-acids in the blood stream and lymph stream, according to my belief, the mother cells of bone marrow and spleen and lymph nodes build up protein of the specific types characteristic of the particular organism, storing it hour by hour in the bodies of unending series of offspring which we call leucocytes and red blood corpuscles. The protein of their bodies will be ultimately discharged into the blood stream, to make up the proteins (globulin and albumin) of the serum, the great common food supply for all the tissues, and an important source of energy for the bodily activities.

What, then, could be more natural than that when there is such depletion of the ranks of the corpuscles through hemorrhage, the cytogenic mechanism should take on exceptional activity, in the effort to make amends for the loss? But, of course, the bodies of the corpuscles, being themselves proteins, cannot be built up without requisitioning a supply of protein-building material and giving out a certain amount of left-over material as nitrogenous waste.

Hence the observed increase in the protein metabolism, after severe hemorrhage—which might, in the light of this theory, have been predicted in advance of the experiment. As to the lack of increase in oxygen intake and carbon dioxide outgo, that only furnishes another piece of incidental evidence that no such number of red blood corpuscles is necessary as that normally

found in the body merely to carry on the work of oxygen conveying. The necessity for an unfailing oxygen supply is so great that provision is made for a supply far in excess of the average needs of the organism, as the bloodletting experiments show.

Without minimizing the value of the services of the red blood corpuscles as a carrier of oxygen, then, we may safely assume that its service as a provider of body protein is at least as great. A realizing sense of the significance of this function comes to us when we reflect that the intricate bodies of the red corpuscles are built up in such numbers, that, massed together, they make up a bulk of about four pounds in the body of a man weighing one hundred and sixty pounds.

So this erythrocytic body surpasses in size every other organ in the body with the single exception of its collaborating organ, the liver. The fact that the individual cells of this great organ are scattered should not have blinded physiologists to the necessity for the assumption that so massive a structure must have vastly important functions in addition to the simple task of carrying oxygen. In point of fact, if the analysis just presented be accepted, it is clear that this anomalous viscus is an organ of the assimilative system having a share in protein metabolism subordinate to no other. The function of dealing with bacterial poisons may, after all, in the widest view, be considered—even as the function of carrying oxygen must be considered—but an incident in the career of the red blood corpuscle.

Its supreme functions are to supply fuel in the form of protein for the bodily activities, and to complete the proteolysis of foreign and native proteins in the blood stream.

Yet the incidental function of aiding the leucocyte to deal with bacterial toxins cannot be considered an insignificant one, inasmuch as the safety of the organism as a whole may at any time depend upon it. Measured in terms of the health of the human individual, and even in human life, this function of the red corpuscle has paramount importance. It would be rash to assert that its defensive and immunizing functions are less constantly called into action or less important in their results than the allied functions of the leucocyte. Both are essential to the life of the organism.

I have suggested, indeed, that the immunizing functions of the two types of corpuscles must be regarded as complementary, rather than as in any sense competitive. It has been suggested also that, to a certain extent, the functions overlap, so that an enzyme secreted by one might facilitate the work of the other. It was tentatively suggested that perhaps opsonin, which so conspicuously aids the leucocyte in its phagocytic functions, may be

produced, partly at least, by the red corpuscles in response to bacterial toxins. But in general it is probably the leucocyte, with its less specialized organization, that aids the red corpuscles, rather than the converse.

As a typical instance, we may note that whenever the red corpuscles are decreased in number—say from vigorous bloodletting—the army of leucocytes at once receives notable accessions, being fully replenished within a few hours. A far longer time will be required to replace the vast coteries of red corpuscles; meanwhile it is the part of wisdom to strengthen the leucocytic outposts. In some cases the numbers of leucocytes may become so great that their bodies must have a really significant share in replenishing the proteins of the blood stream, thus making partial amends in this direction also for the paucity of red corpuscles.

The Leucocytic Balance

The consideration of such fluctuations in the ranks of the corpuscles naturally raises a question as to how the leucocytic balance is maintained.

We know that under average conditions of normal health the number of leucocytes in the blood stream averages about six thousand to the cubic millimeter, rising to about eight thousand three or four hours after a hearty meal; and that the number of red corpuscles averages about five million to the cubic millimeter and is less subject to wide variations in times of health.

These facts are so familiar that we scarcely think of them as requiring explanation. Yet a moment's consideration makes it clear that the maintenance of the corpuscular balance is a very puzzling phenomenon.

How are the mother cells in the bone marrow and spleen, for example, to know that protein foods have been taken into the stomach, and that therefore an additional supply of leucocytes is needed? How are these mother cells to know that there has been a great destruction of red corpuscles in the liver; or that a wound in some remote part of the body has resulted in a severe hemorrhage? How are they to know that a colony of pneumococci has found lodgment in the lungs, and that fresh bands of phagocytes are required to fight them? How are they even to know that the body is undergoing vigorous muscular exercise; or that a cold bath has been applied to the skin?

These surely are interesting questions. Under all the conditions just noted, the cytogenic cells do, in point of fact, take on exceptional activity, and produce leucocytes in particular in unwonted numbers.

But where is the census-taker of blood corpuscles who has signaled to them that these exceptional recruits are needed?

The more one considers that problem the more puzzling it seems; particularly in view of the fact that the bone marrow is but doubtfully connected with the nervous mechanism. There are sympathetic nerves in connection with the blood-vessels, to be sure, and these might serve to modify the blood supply; but we can scarcely suppose that this by itself can control the activities of the cytogenic cells, particularly if we recall that the blood-pressure may be increased indefinitely without necessarily causing leucocytosis; whereas, on the other hand, active generation of leucocytes may occur after a hemorrhage that has reduced blood-pressure to the minimum.

It does not necessarily follow from this that the sympathetic nervous system may not have a share in determining the activities of the cytogenic cells. The nervous mechanism may well be supposed to take part in the co-ordinating of the activities of the various mother cells, located in bone marrow and spleen and widely scattered lymph nodes. But there is another and quite different stimulating and co-ordinating mechanism which recent studies have brought into the foreground, namely the endocrinous system, with its various internal secretions and hormones.

The messengers of this system travel in the blood stream itself, as also doubtless in the lymph stream, and there is a good deal of evidence pointing to these agents as the stimulators and regulators of cytogenic activity.

I have had verbal report from a colleague of cases of diabetes and Graves' disease, in which the therapeutic exhibition of the duodenal hormone, *secretin*, is reported to have led to a rapid and extraordinary rise in the blood count, including both leucocytes and erythrocytes. It is interesting to note, as strongly supporting the Proteomorphic theory, that this corpuscular increase is said to have coincided with very marked amelioration or total disappearance of the symptoms of protein poisoning that characterize the disease. But at the moment our attention is directed to the probably direct connection between the exhibition of secretin and the increased activities of the cytogenic cells.

It has been clearly demonstrated that secretin, as produced in the duodenum, enters the blood, and being carried to the pancreas, stimulates that organ to the production of its characteristic tryptic enzymes. What more natural than that the same hormone should carry similar messages to the bone marrow to stimulate the production of the leucocytes that are known to secrete an enzyme closely allied to trypsin, and to subserve,

within the vascular mechanism, a function of proteid digestion comparable in a small way to that of the pancreas itself?

In the activities of the hormone secretin, then, if these inferences are justified we find a solution of one aspect of the problem of maintenance of the corpuscular balance. This duodenal hormone being available as a messenger, the fact that the tissues of the bone marrow take on fresh activities in response to the taking of food into the stomach seems no longer mysterious, or at least no more mysterious than, for example, the increase in the activities of the pancreas brought about through the same agency.

There are other conditions, however, in which there is increase in the blood count, where the agents through which the cytogenic mechanisms are stimulated may not be so readily traced. How, for example, shall we explain the leucocytosis that takes place in the course of violent muscular exercise?

Here the explanation offered must be regarded as altogether theoretical and provisional, although assuredly not lacking in plausibility. The suggestion I would make is that the increase of leucocytes here is due, in part at least, to the increased flow of lymph resulting from muscular contraction. It is known that lymph scarcely flows at all in the lymphatics of the limbs during quiescence, but is stimulated by active or even by passive movement. It is known also that lymph flowing through a lymphatic gland is observed to emerge with an increased increment of leucocytes, and the inference seems unavoidable that the leucocytes in question were developed in the lymph node. It is a fair inference that their rate of development depends on the rate of flow of the lymph which must bring the food albumen to their mother cells, and if this be admitted the increase in such of the leucocytes as are developed in the lymphatic system as a result of muscular exercise is accounted for.

The function of the lymphocytes thus brought forth would be, perhaps, to assist in the catabolism of products of protein decompounding associated with muscular activities (e.g., creatinine) or of materials (proteins or fats) for supplying foods or fuels to these cells. In the original presentation of the Proteomorphic theory it was suggested that this lymphocyte assists in the decompounding of the normal serum proteins. I am now disposed to question the validity of this assumption, but there were certain collateral suggestions that perhaps warrant reproduction of the paragraphs in question here:

"A word should be said about the precise service which the lymphocytes thus called forth in response to muscular action render to the muscles that have indirectly engendered them. This lymphocyte is not a phagocyte, but it may have to do with the

decompounding of the normal proteins of the blood serum (globulins and albumins). These are decompounding to make fuel (including a large proportion of glycogen) to supply energy to the body-cells, and notably (1) to the digestive apparatus, or (2) to those most important dispensers of energy, the muscle cells.

"I have suggested that the activity of the muscle cell is conditioned on an increase of osmotic pressure due to a decompounding of the protein within the cell. This is necessarily accompanied by loss of energy, expended as mechanical energy and as heat. The physical contents of the cell are for the most part not wasted, but they cannot be recompounded into proteins except through the agency of energy supplied from without. The molecules of serum protein, suspended in blood stream and tissue fluids, are decompounded to supply this energy. And, according to the present view, the lymphocyte is the agent (or at least one of the agents) supplying the enzymes that inaugurate this process of decompounding.

"Hence the urgent necessity for an increased supply of these leucocytes in times when the muscles are called upon to undergo excessive contraction for prolonged periods.

"Hence, also, the necessity for an increase of lymphocytes after the ingestion of food, to aid in the decompounding of serum proteins to supply fuel for the activities of the glands of stomach and pancreas and upper intestines. It is to meet this need that the lymphocytes are observed (as we have seen) to be sent out in greatly increased numbers during digestion. The supply of digestive ferments cannot be made out of nothing. The cells of the digestive apparatus cannot keep up their activities unless they are supplied with energy from without. It is the province of the serum proteins to supply this energy, in part at least, here as in the case of the muscles and other tissues; and the lymphocytes, according to the present view, have a share in bringing about the decompounding of the serum proteins, through which their energy is liberated and made available.

"Should the numbers of the lymphocytes seem inadequate for such a task, it may be pointed out that their work is the relatively simple one of tearing to pieces an unstable molecule. Possibly nothing more is required than to seize on a single group containing the protein molecule's three sulphur atoms to send the entire structure, with its thousands of carbon hydrogen, oxygen, and nitrogen atoms, tumbling.

"Incidentally, attention may be called to the curious interest that attaches to the observation of the cyclic co-ordination of parts evident in the observed fact that the lymphocytes which (in this view) aid indirectly in the production of the digestive

ferments, are themselves called into being through a stimulus to their mother cells sent out as a hormone messenger from the digestive apparatus itself.

"Similar cycles of co-ordination, however, are not unusual in the organism. Indeed, the case just cited of the lymphocytes developed in the lymph nodes through the action of the muscles, and in turn serving presently to aid the muscles that indirectly engendered them, furnishes us another and no less striking illustration of such an harmonious dual alliance."

Hormones and the Corpuscle-balance

I shall not here discuss in detail the rationale of operation of the remaining causes that are observed to promote leucocytosis, which include cold baths on one hand and fevers of microbic origin on the other; contenting myself with the suggestion that the cold bath stimulates the vasomotor apparatus of the sympathetic system; and that the bacterial toxins, when present in the body fluids, doubtless stimulate the cytogenic apparatus directly, while the bodies of the bacteria serve as a food pabulum for the leucocytes that may lead to the proliferation of the latter through cell division.

The normal leucocytosis of pregnancy may also be dismissed with the remark that it furnishes, in view of the known invasion of the blood by foreign (placental) protein, strong corroborative evidence for one phase of the Proteomorphic theory.

It seems desirable, however, to speak a little more in detail (though still very briefly) of the part in maintaining the corpuscular balance, and in determining the activities of the leucocytes, that appears to be played by the endocrinous organs; in particular by the adrenal bodies, the thyroid apparatus, and the glands of the duodenum.

To establish a strong *a priori* probability that some at least of the internal secretions directly stimulate the activities of the corpuscles, it is only necessary to appreciate the fact that the corpuscles themselves must be classed among the important members of the endocrinous system; and to recall that the products of the various ductless glands are observed to interact in mutual stimulation and inhibition of the organs that produce them.

When, therefore, to cite a specific instance, it is observed (as in Cannon's experiments) that a sudden increase in the adrenal secretions, induced by an emotional state of fear or anger, results in an immediate increase of glycogen in the blood, in preparation for active muscular exertion, we may justifiably infer that the increase has been brought about, in part at least, by stimulus to the enzyme forming functions of the lymphocyte, induced by

the presence of unusual quantities of adrenalin in the medium in which the lymphocyte is suspended.

Again, the observed fact that persons suffering from hypothyroidism are unduly susceptible to the attacks of bacterial diseases, finds suggestive explanation in the theory that a normal supply of thyroidin is essential to the normal functioning of the cytogenic apparatus. Moreover, there is a certain amount of direct evidence for the claim that the exhibition of thyroid extract promotes cytogenesis.

An increase of proteid metabolism has been observed in cases of exophthalmic goiter; and the experiments of Anderson and Bergman show a similar increase from the giving of large doses of thyroid extract. If the rôle of the corpuscles in proteolysis here presented be accepted as valid, these observations would form another bit of presumptive evidence linking the thyroid apparatus with the cytogenic mechanism.

General Therapeutic Applications of the Proteomorphic Theory

To the clinician it perhaps does not so greatly matter as to what theoretical explanations are given of the relations of hormones or other agent to the stimulation of the cytogenic system. It suffices to know that there are certain available agencies through which the production of corpuscles may be stimulated; and through which, therefore, according to the present theory, the processes of normal protein metabolism and incidentally, but most importantly, the immunization of the patient against bacterial diseases, and the cure of these diseases themselves, may be facilitated. What these agencies are has been suggested in the course of the preceding discussion.

It remains now to make a few practical suggestions as to the utilization of these agencies; and, in general, as to the benefits that may accrue to the patient through recognition, on the part of the physician, of the principle that the blood corpuscles, white and red, are the all-important agents in the fight against bacterial diseases.

Let us take as a typical illustration—because the most common and familiar—the case of a patient suffering from tuberculosis.

The tubercle germ invades practically every human organism. But so well defended is the average system against its attacks that ninety per cent. of all the individuals of a given generation are able to throw off the invader, and attain full individual immunity to its attacks. Such immunity, conditioned on the

hereditary status of the germ-plasm, is passed on to the offspring of the individual.

But ten per cent. of the individuals of each generation are not able thus to ward off the attacks; on the contrary, they succumb to it, and after all their tissues are devitalized to an extraordinary degree, they ultimately die. Their failure to fight off the germs is, of course, due to an inherent lack in the make-up of their defensive mechanism. The mechanism in their leucocytic and erythrocytic apparatus that should produce anti-ferments against the tubercle germ is either altogether absent or is devitalized and minimized in efficiency. The result is that their tissues are in a condition comparable to that which the student of anaphylaxis speaks of as "sensitization," and which I have suggested, should be considered merely as lack of defence. Regardless of the precise terms of the explanation, they are susceptible to the attacks of the germs, and this inherent susceptibility may be passed on to their offspring.

It is of important, even if of incidental, interest to recall that, according to the recent studies of heredity, this susceptibility appears to act as a Mendelian recessive.

That is to say, a susceptible person, mated with a normal or resistant person, will have offspring that are normally resistant, but who contain in their germ-plasm, as a recessive tract, the factors of susceptibility or lack of immunity. If such personally resistant, but potentially susceptible, individuals are mated, one of their offspring in four, on the average, will be susceptible. This is of great importance from the standpoint of the eugenist, but need not be considered further in the present connection.

Suffice it, for the present, that even the susceptible person is susceptible only in a relative sense, and is by no means altogether without a defensive mechanism. His chief danger may lie in the fact that his cells are partially habituated to the presence of this toxin, and therefore will not respond to it actively.

If we inquire what can be done to stimulate the defensive response, we are at once reminded of the methods that lead to an increase of the numbers of the leucocytes in the blood. The ingestion of hearty food, notably protein, leads to such increase. Active exercise leads to such increase. Cold baths stimulate such increase. Nourishing food in the largest quantities that can be assimilated; exercise of a fairly vigorous type, and hydrotherapy would seem to be theoretically indicated. Also fatty foods to conserve the protein, and iron to facilitate production of hemoglobin. No practical physician needs be told that these measures have been shown empirically to be of the greatest value in the treatment of tuberculosis.

Recent experiments have shown that air at very low tempera-

ture has a stimulative influence similar to that of the cold bath. This observation seems to explain the familiar clinical fact that tuberculosis may be treated advantageously in very cold climates. The results of sleeping in the open air in an almost arctic temperature are familiar to clinicians. The cold temperature is probably as directly beneficial as the fresh air itself.

As to exercise, practised before the patient reaches a stage of asthenia that makes it dangerous, the beneficial results are equally little in doubt. Mountain climbing, with attendant fatigue falling just short of extreme exhaustion, is a recognized therapeutic measure of the utmost importance. In all probability, the climbing rather than the mountain air produces the benefit.

Incidentally we may note, in confirmation of the view of erythrocytic activities here presented, that the blood is thicker at high altitudes, so that the red corpuscles are relatively more abundant and hence patrol the blood better; but that the total amount of hemoglobin is not correspondingly increased (Viault, Abderhalden).

The value of the cold bath has long been recognized by a few astute clinicians, who have found it difficult to gain headway for their views partly, perhaps, because the *rationale* of the benefits to be expected has hitherto been obscure. The knowledge that the cold bath directly stimulates the production of an additional army of leucocytes; coupled with the belief that the leucocyte is the pre-eminent agent of immunization against the direct invasion of bacilli, furnishes the all-sufficient answer. The cold bath may have other beneficial effects, but this one alone justifies its use in all bacterial diseases in which there is an inherent tendency to defective leucocytosis.

A striking illustration of the value of the cold bath is furnished in the reports of the Munich military hospital, in which records of more than eight thousand cases show that since the cold bath was used habitually in the treatment of typhoid fever the mortality of that disease was reduced from forty-two per cent. to three per cent.

As to the matter of a liberal diet, there would be no difference of opinion in the case of the consumptive, but opinions might differ, and undoubtedly would differ, when acute fevers are in question. Indeed, the old familiar rule to "starve a fever" has been an axiom upon which the average physician has acted somewhat persistently. But it has recently been suggested by Coleman that this rule is perhaps as fallacious as the other rule, now fortunately abandoned, that the fever patient should be deprived of water as well as of food. Coleman reports gratifying results in typhoid fever cases in which a liberal diet was provided. "Not

only is the course of the disease favorably influenced," he says, "but the condition of the patient is vastly improved."

And these recent observations are, after all, only confirmatory of experiments conducted by Von Hosslin more than thirty years ago, which showed the value of a liberal diet in ordinary fevers.

If we ask why a liberal diet, including proteins, is essential in the treatment of fever, the answer is not far to seek. According to theory, the leucocytes and red corpuscles fight the invading proteins and enzymes by constantly putting out chemical compounds that antagonize them by cleaving their complex molecules on one hand and by combining them into new and harmless associations on the other. But this constructive work on the part of the corpuscle implies the expenditure not merely of energy, but of matter. And material for this expenditure must in some way be found to make up for the constant depletion.

The corpuscles can no more be expected to perform their work without being supplied with fuel than can any other machine.

Nor can new corpuscles be developed to fill the constantly decimated ranks without drawing on an unfailing supply of proteins. And unless this material is supplied in the pabulum that comes from the outside world, usually through the medium of the intestinal canal, it must be found elsewhere. And obviously the only other source is the body tissues themselves. So if the defending hosts are not supplied with food pabulum from without, they must draw on the tissues of the body, with a weakening effect. Hence the rapidly emaciating effect of fevers, with attendant weakness; an effect largely avoided through use of a liberal diet.

It will be understood, of course, that the catabolic activities of the leucocyte and red corpuscles, in which complex protein molecules are constantly cleaved to smaller molecules and arranged in new combinations, must be attended by a constant liberation of heat. So the fever itself is in part an evidence of the activities of the corpuscles. And liberal feeding, provided the food is assimilated, may unquestionably tend to enhance the fever.

But the modern clinician does not regard fever as in itself necessarily disadvantageous to the patient. On the contrary, he associates it with the immunizing and curative processes in the body. So he does not regard a rise in temperature as necessarily an evil. He knows that the phagocytic activities of the leucocytes are greatly accelerated when the temperature is high; the leucocytes have been observed at increased temperatures to "dart about like bees around a hive." It may reasonably be inferred that the chemical activities of all the immunizing agents are correspondingly accelerated.

Nevertheless there are dangers in excessive temperature, if for no other reason because tissues that it is essential to conserve are also stimulated thereby to unwonted activity. So it is highly desirable from time to time to accelerate the removal from the body of the excessive heat due to the chemical activities. And, of course, the best practical means of accomplishing this is the cold bath.

The idea of giving a fever patient liberal potations of water, feeding him freely with nourishing foods, and from time to time plunging him into cold baths or swathing him in cold packs would have come very near to giving an apoplectic shock to the best clinicians of a century ago. But nowadays such procedures have the fullest experimental or clinical warrant, and find explanation in the data of physiological chemistry.

It is probable, however, that comparatively few clinicians among these who use the cold bath habitually in fever cases, and recognize its value in the direct reduction of temperature, take cognizance also of its significance in stimulating the cytogenic organs to the production of new hosts of germ destroyers. Yet it is probable that the latter is by no means the least of the services performed by the cold bath.

It is a little difficult to accustom one's self to the idea that there is no necessary connection between the degree of fever and the virulence of intoxication. But the truth of this proposition is suggested by the familiar observation that infants often show a high temperature when their maladies are comparatively mild. And it receives experimental demonstration through the observations of Vaughan and others to the effect that small doses of a protein poison may cause a rise of temperature in animals where far larger doses of the same toxin produce no fever, but may even cause a fall in temperature.

Vaughan very justly refers to this as a puzzling and not clearly explicable fact. A conceivable explanation might be that small doses stimulate the defensive leucocytic mechanism, while large doses act with such suddenness and violence as to paralyze them; just as they sometimes seem to be helpless when they have ingested a large number of toxic bacteria. It should be recalled that the introduction of these large doses of foreign proteins directly into the vascular system is a phenomenon that would be of exceeding rare occurrence outside the laboratory. The fang of a serpent is about the only mechanism in the natural world that would be capable of introducing a foreign protein in quantity into the animal system. So the defensive mechanism has not often been called on to reckon with this contingency, and it cannot deal effectively with excessive doses of toxic proteids.

But, however explained, these laboratory experiments are of

great value in teaching the clinician that he must not depend too fully on his clinical thermometer as a guide to the virulence of disease.

As to pharmaceutical agents calculated to stimulate the activities of the cytogenic system, mention was made in the original presentation of the Proteomorphic thesis, of secretin, of thyroid extract, of powdered spleen, and of bone marrow. Doubtless these agents have a measure of utility, but in the light of recent experience they assume an altogether subordinate rôle. The parenteral injection of non-toxic proteins has been shown to offer therapeutic possibilities scarcely more than adumbrated by any stimuli to the cytogenic apparatus hitherto known. These possibilities are forecast in the general treatment of the theory of antigenic response in the original presentation of the Proteomorphic theory.

The details of their application, through the development of Proteal therapy, will form the subject matter of most of the succeeding chapters of this book.

Serums, Vaccines, and Direct Cyto-therapy

Of specific serum and vaccine therapy in general I shall speak only in the most general way, although reference to the non-specific elements always necessarily involved will be made in another connection. By way of anticipation, however, there are one or two aspects of the subject that may advantageously be given brief consideration here, from the standpoint of the Proteomorphic theory.

Consider, for example, the observation of Dr. W. H. Park, to the effect that when a horse having a strongly antitoxic blood is injected intravenously with a definite amount of toxin, very little production of antitoxin takes place, because the toxin is neutralized by the antitoxin in the blood, whereas the same amount injected in scattered spots subcutaneously will produce a large amount of antitoxin. Dr. Park argues, logically enough, that such portions of the subcutaneously injected toxin as come into the blood stream will meet the same fate as that injected intravenously. He concluded, therefore, that some or all of the cells in the area in the subcutaneous tissues that the toxin reaches must take part in producing antitoxin.

This conclusion is obviously in harmony with the Proteomorphic theory, which postulates that body-cells of many types may on occasion respond to the invasion of toxins of the polypeptid order of chemical complexity. It should be recalled, however, that white and red corpuscles are everywhere within reach, in more or less static capillaries and tissue fluids, and that their

services may have been available, even though the injection was not made directly into the blood stream.

Again in Sir Almroth Wright's application of vaccine therapy to localized infections already in being, such as boils, and even to general infections, including typhoid fever, the injection is usually subcutaneous or intramuscular, not intravenous, but it is obvious that the leucocytes residing at the moment in the static tissue fluids and lymph spaces are brought directly into contact with the invading bacteria (in this case dead, but laden with their foreign proteid). They are seen to accumulate and to attack the dead bacilli actively, and we can hardly doubt that they are directly stimulated to send out antidotes—complement, opsonin, bacteriolysin—that presently percolate into the general blood stream and are carried to the special tissues where the invasion of living germs is taking place.

In this case the locally injected germs are unquestionably attacked and largely engulfed by the local garrisons of leucocytes, and it is difficult to conceive what other agent can be responsible for the secretion of the antibodies with which the blood presently becomes infused.

Although it seems almost unavoidable to conclude, in such a case as this, that the white blood corpuscle is the agent of antibody production, where protein poisons are in question, yet the conclusion, after all, is inferential only. Some remarkable experiments have recently been made by J. W. Vaughan, however, in which the genesis of specific enzymes in the body of the leucocytes in response to protein poisoning, is demonstrated.

In these experiments, as recorded by Victor C. Vaughan, the inoculation of sheep or rabbits with finely ground cancer tissue led to the rapid increase of large mononuclear leucocytes in the blood, until they reached twenty-five per cent. or more of the entire leucocytic population. The animal is then bled, the blood is laked with acetic acid, and the leucocytes are collected in a centrifuge. They are rubbed with sterile sand in salt solution and passed through a Berkefeld filter.

It is found then that the filtrate contains the specific proteolytic ferment which splits up cancer cells.

"This is shown by incubating it with cancer cells, when the poisonous portion of the protein molecule is freed, as is shown by the fact that when injected in the fresh rabbit it causes sudden death. Incubated with other proteins, the leucocytic extract liberates no poison. This leucocyte extract when injected in certain amount directly into cancer tissue produces anaphylactic shock."

The experiment led the elder Vaughan to conclude that "this work seems to indicate that the specific enzyme for cancer cells

is furnished by the large mononuclear leucocyte." Another interpretation is possible, as I shall show presently, but the experiment justifies the conclusion "that in work of this kind lies a promise of at least partially insulating the anaphylactic enzymes and studying their effects."

"Anaphylactic enzymes," it will be understood, is the term used by Vaughan to describe the so-called antibodies put out in response to foreign proteins, about which we have all along been speaking.

This experiment certainly shows that in some cases the leucocyte may be the agent of origin, or at least of transfer, of the antibodies directed against poisons. It should be added, however, that the elder Vaughan does not ascribe this function exclusively to the leucocytes, for he expressly states in another connection that it is possible that the protective enzymes are formed by different cells according to the "sensitizer" (i.e., the proteid toxin) used—a view obviously in harmony with the proteomorphic theory, though far too general to be cited as specifically supporting the theory.

In the original presentation of the Proteomorphic theory it was noted, in pursuance of this aspect of the subject, that Vaughan was then testing his extract of mononuclear leucocytes in the treatment of cancer, and the following comment was made, which has peculiar interest in the light of more recent developments: "Whatever the immediate results of this particular test, there is every reason to hope that the method inaugurated, in which the leucocytes are directly looked to for the production of immunizing enzymes, will be generalized and given an important place in therapeutic procedure in the near future. It is a short step from the clear conception that the leucocytes are the chief agents in the producing of immunizing ferments to the direct utilization of the leucocytes themselves in therapeutic procedure.

"That an antidote thus prepared may have marked advantages over an antitoxic serum is clearly suggested in the work of Vaughan just referred to. For he found it impossible to use the serum of a 'sensitized' animal, because, in the first place, repeated injections of the serum caused albuminuria; and, in the second place, they 'sensitized' to the proteins of the serum. The leucocytic extract also 'sensitizes' to the blood serum, until it is passed through a Berkefeld filter, after which it is innocuous. All of which may readily be interpreted in terms of the Proteomorphic theory.

"Here, then, is at least a strong suggestion of the possibility of producing antibodies directly from the filtered bodies of the leucocytes, and avoiding the danger of serum disease which is

well recognized as attendant on the present method of serum therapy and which sometimes has such alarming results."

I wrote these words in September, 1914. Following them I presented a recapitulatory summary of the essentials of the Proteomorphic theory, concluding with these words:

"The general theory of the action of the cytogenic system above outlined finds support in clinical observations of disease and in empirical therapy; and the theory itself gives important clues to the scientific application of old and new therapeutic measures, including an extension of serum-therapy and vaccine-therapy and the development of a new cyto-therapy.

"Such, then, are some of the salient aspects of the Proteomorphic theory of immunization; a theory which postulates the cytogenic system as the chief immunizing mechanism, and its daughter cells, the leucocytes and red corpuscles, as the active direct agents in carrying out the beneficent functions of that mechanism.

"It is not claimed that a complete demonstration of the truth of this theory in all its aspects has been presented, nor that such demonstration is possible with data at present available. Nor can it be supposed that all parts of so novel a theory have been correctly conceived. Yet, even as presented, it would appear that the theory throws light into a good many dark places of the realms of physiology and pathology.

"In any event, I feel that the fundamental concept of the theory has been made sufficiently plausible to justify, and indeed to demand, a far larger share of attention for the leucocyte and the red corpuscle on the part of bacteriologist, pathologist, and practicing physician than has hitherto been accorded these small but highly important bodies."

The story of the development of the "new cyto-therapy" thus adumbrated, under guidance of the Proteomorphic theory, has been told in part on earlier pages of this volume, and will be further elaborated in succeeding chapters.

CHAPTER III

THE DISCOVERY OF THE PROTEIN PRINCIPLE IN THERAPEUTICS

Shortly after the first publication of the Proteomorphic Theory (*American Medicine,* October and November, 1914), I was in Baltimore and had opportunity at Dr. Howard Kelly's private sanitorium to see a number of cancer cases undergoing radium treatment. I was also shown photographs some of which revealed really spectacular modifications of malignant growths under influence of radium, and I received first-hand accounts, from physicians not directly connected with the work, of cases in which cancerous growths had magically disappeared apparently as a direct result of the application of radium.

These observations interested me profoundly, and from many points of view. Not long before I had visited Professor Ernest Rutherford in his famous laboratory at Manchester, and had been permitted to study at first hand his radium apparatus, and to observe his fascinating experiments. I had visited Sir J. J. Thompson at the Cavandish Laboratory in Cambridge, at the time when he was making his first photographs of atoms in the vacuum chamber. I had visited Lenard, the precursor of Roentgen, at Freiburg; and Ostwald at his home in Grossbothen; and Arrhenius at the Nobel Institute in Stockholm; and Zeeman in his wonderful laboratory at Amsterdam; and had discussed the alluring problems of the ultimate constitution of matter, the relations of matter and energy, the character of chemical action and electrical action, and kindred subjects suggested by the different yet closely allied discoveries for which these men are famous.

I had also visited and talked with a group of discoverers in the biological field, and similarly attempted to correlate their observations—for example, Metchnikoff, at the Pasteur Institute in Paris, who was then studying conditions in the alimentary tract in their relation to health and longevity; Ehrlich, at his Frankfort Institution, who had just given the world salvarsan, and thereby revived hope in specific chemo-therapy; Sir Almwroth Wright, at St. Mary's Hospital in London, who was actively elaborating the theory and practice of autogenous vaccine therapy, and venturing into another new field in the attempt to combat hay fever with pollin extracts; and Professor George F. H. Nuttall, Quick Professor Biology at Cambridge University, whose fascinating work with the precipitins, through which

he had tested the genetic relationship of hundreds of species of animals, had recently won him Fellowship in the Royal Society—a distinction shared, I believe, by no other American.

With the work of these men I had, of course, long been familiar. Some of the men I had known for years, and visited on previous occasions. But at this time I was making an especial effort to correlate the new advances along different lines of science in the fields of physics, chemistry, and biology. A little later I sought, through correspondence, the opinions of a thousand leading men of science, actual workers in one field or another, as to what, in their judgment, was the most important unexplored or half-explored field just ahead. By co-ordinating these diversified opinions, I thought to attain a clearer view than had hitherto been possible of the trend of scientific thought in our day and the probable eventualities of the new scientific era on the threshold of which we stand.

It was these studies, doubtless, combined with the earlier investigations that had found expression in my *History of Science*, that made possible the crystallization of ideas in my mind represented by the Proteomorphic Theory. The actual textual formulations of that theory at the particular time when it was written came about through the accident of my being asked to make a summary of existing theories of immunization. The mental co-ordination through which the new and in a sense revolutionary tenets of the Proteomorphic Theory flashed into my mind eventuated, rather curiously, one evening as I sat at dinner with my daughter in a little restaurant down in 11th Street. The dictating of the twenty-five thousand words of copy comprised in the presentation of the theory in *American Medicine* was a *tour de force* begun and completed in the leisure hours of three or four consecutive days.* But the connotations of the

*I would not seem to imply that the writing of this amount of matter in the time mentioned constitutes an unusual task. A few months before the Proteomorphic theory was written I had dictated more than half a million words of finished manuscript (making eleven fair-sized volumes) and turned the manuscript over to the printer in a period of *fifty consecutive days*. On almost numberless occasions I have written from twelve thousand to fifteen thousand words of finished manuscript per day for days together. One of my large books was begun on Monday morning and finished Saturday night of the same week. Another (Volume I of my *History of Science*) was produced in the midst of exacting duties of a different character by dictating one hour daily (eight to nine in the morning) for twenty consecutive days. I mention these incidents to illustrate an habitual tendency to concentrated mental action, in explanation of the seeming anomaly that so comprehensive and even revolutionary a doctrine as that comprised in the Proteomorphic theory should have been produced rather as a mental pastime than as a fixed task. I may add, however, that the aftermath of the "mental pastime" in question has involved me in a series of laborious investigations, of which this volume gives some intimations, that will probably occupy a large part of my time for the remainder of my life.

theory, and the mental associations that made its elaboration possible, represented a lifetime of study; and the sequential developments, to which I am about to refer, were equally conditioned on antecedent knowledge acquired through years of investigation. It is in this connection that I call to mind the otherwise unrelated incidents just cited.

In particular, I would recall that the thing that impressed me most in the visit to Ehrlich, above mentioned, was the room in his laboratory where endless series of glass jars contained cancerous mice. Ehrlich himself at the moment was all enthused over his tentative success with salvarsan, and he made but incidental reference to the cancer mice, but I felt that this was the problem that would next engage his attention—a problem, indeed, that had been interrupted by the other studies. With peculiar interest, then, I learned a little later of the experiment in which he had attained at least tentative results in the development of a chemical combination, including selinium, that appeared to have a selective action on cancer cells; a work duplicated, independently, I believe, by Wassermann, in Berlin.

These observations, and the still newer work of Wassermann, in which he had endeavored to diagnose the presence of cancer by tests applied to the blood, were fresh in my mind when I observed the patients, and studied the photographs, at Dr. Kelly's sanitorium there in Baltimore. I had also in mind the recently reported experiments of Dr. Leo Loeb with colloidal copper in the treatment of cancer. And I was, of course, familiar with various tentatives in cancer treatment that had been made with biological products, as admirably summarized in Dr. Bainbridge's book of which just at this time I received a presentation copy from the author. In particular I had followed with interest the work of Hodenpyl, partly because I chanced to know personally the patient from whom the ascitic fluid used by him with such thought-provocative results was removed.

And as I linked and co-ordinated these various items of knowledge, the thought that was paramount in my mind was that, beyond preadventure, it had been demonstrated that the cells of a malignant neoplasm, notwithstanding their similarity to normal cells, have essential differences that bring them within the possibility of selective action on the part of physical or chemical agencies. The fact that all the methods of practically treating cancer used hitherto had proved only tentative or utterly disappointing; the fact that the cancer mass seemingly dispelled by radium treatment might recur and grow with renewed and fatal activity—these facts seemed to me altogether subordinate to the great central fact that the cancer cell could, in some instances, be caused to undergo seemingly autolysis through the

application of agencies that were not necessarily destructive of the normal tissues subjacent to the abnormal growth.

This possibility being demonstrated, it seemed to me that the first great step toward the ultimate successful issue of the contest with cancer had been taken.

It appeared to me, however, that radium therapy, as applied to cancer—and the allied X-ray treatment which I had also investigated—was subject to one almost insuperable difficulty. It was hard to conceive how a method could be devised through which the application of the disruptive rays could be brought to bear on the cancer cells without bringing an influence on the cells of healthy subjacent tissues; and there was ample clinical evidence that if this influence was carried beyond a certain stage injury resulted to the healthy cells no less than to the abnormal ones. The fair inference seems to be that the cancer cells are of somewhat less stable constitution; that they, therefore, yield more readily to the disruptive influence of the radiation; but that the difference between these cells and the normal cells in this regard is a difference of degree and not a difference of kind. Such being the case, there is an obvious obstacle in the use of radium or the X-ray, which by no means bars these agents from usefulness, but which suggests, as it seems to me, that they do not give promise of ultimate ideal solution of the problem.

The ideal would be a chemical agent, biological or other, that had selective chemical affinity for the cancer cell, with capacity to effect disruptive activities, somewhat as salvarsan seemingly has selective affinity for the spirochaete of syphilis.

In particular, at this time, my mind dwelt on the experiment of Vaughan, with a brief statement of which the original presentation of the Proteomorphic Theory had been concluded, which showed that the large mononuclear leucocyte produces or contains enzymes capable of splitting up cancer cells. In the concluding paragraph of the Proteomorphic Theory, as originally published, I suggested the possibility of producing antibodies from the bodies of leucocytes; and I had in mind, naturally, the possible application of such enzymes in the treatment of cancer (it was well known that Vaughan was working practically along these lines), and also the more general application of the method implied in a predicted "extension of serum therapy and vaccine therapy and the development of a new cyto-therapy."

That the suggested new therapy involved the use of measures to increase the numbers of corpuscles, and stimulate their enzymic activities, was everywhere implied, and moreover was explicitly stated in the discussion of agents calculated to produce this effect; but the simple method of evoking a corpuscular response by parenterally introducing foreign proteins as such did

not occur to me until later—although the idea lies so near to hand that, looking back, it would seem that it must inevitably occur to any one who grasps the fundamental features of the Proteomorphic Theory. But here, as so often elsewhere in the field of discovery, the retrospectively obvious may not be obvious to all from the contemporaneous standpoint.

Nevertheless the idea was apparently very close to the surface of my mind, for it came into clear view, as a vivid reality, a little later, and was given concrete and tangible expression in the paper that I published in the *New York Medical Journal,* October 2, 1915—just a year after the original publication of the Proteomorphic Theory.

The specific observations that led to the clear realization and application of the Proteomorphic principle had to do with a series of cases of cancer, part of which had come under my direct personal observation, and the remainder under observation at second hand, so to speak, through personal correspondence with the physicians who treated them. The treatment consisted of the hypodermic injection of a vegetable extract, the nature of which was not at first very clearly divulged, but which was ultimately known to be produced by macerating a dozen powdered plant substances in salt solution or in alcohol. The substances in question, as ultimately revealed, were the following: *Menyanthes trifoliata,* buckbean (leaves); *Melilotus officinalis,* sweet clover (leaves); *Mentha crispa,* mint (leaves); *Brassica alba,* mustard (seed); *Anemone hepatica,* liver leaf (leaves); *Viola tricolor,* pansy (flowers and leaves); *Anthemis nobilis,* camomile (leaves); *Citrullus Colocynthis,* colocynth (fruit); *Quassia amara,* quassia (wood); *Urtica diocia,* nettle (whole plant except root); *Rheum officinale,* rhubarb (root); and *Hyssopus officinalis,* hedge hyssop (whole plant except root).

The formula for this bizarre compound, of unrevealed origin (and now having only historical interest), had been brought to this country by a Hungarian layman and used originally as a poultice in the treatment of superficial epitheliomas and carcinomas. The extract in question, made at the instance of some New York physicians who became interested in the matter, was used hypodermically, and at first injected directly into the cancer mass, the observed effect being supposed to be local.

My attention was called to the matter in February, 1915, soon after I had observed at first hand the effects of radium in the treatment of cancer in Dr. Kelly's sanitorium as above related, and at a time when my mind was actively engaged in considering various aspects of the cancer problem, and of the possible application of the Proteomorphic Theory. It is speaking within bounds to say that I was profoundly impressed with what I saw of cases under treatment with the vegetable extract at

the Polyclinic Hospital in New York. The clinical results, particularly in a case of cancer of the rectum and a case of hypernephroma, struck me as spectacular and in the highest degree thought-provocative.

But I was impressed also with the observation that—in these cases and in various others—there appeared to be a congested condition in the region of the tumor masses, involving both white corpuscles and red, that was at least inferentially associated with the autolytic process.

Meantime the action of the extract was not that of an escharotic. This was fairly obvious even at the outset, when injection was made directly into the tumor masses; but it became demonstrative when it was found a little later that the hypodermic injection could be made into distant regions of the body —say, the upper arm—with apparently the same results in localized action on a tumor of the breast, the uteras, the stomach, or other region. This seemed to imply a selective action as between cancer cells and normal cells; and the observations on the blood appeared to justify the inference that the corpuscles were the effective agents through which the selection came about.

Such, at least, was my own inference, biased as I naturally was by what may be called the Proteomorphic point of view.

Coupled with the collateral observations outlined above, the matter seemed to be of sufficient importance to merit very careful investigation. I made such investigations in the offices of the New York physicians who were applying the treatment, and through correspondence with numerous others. I also visited a physician in a neighboring city, who had twenty-five or thirty cases under treatment, carefully inspecting the cases. In the aggregate, the cases that came under my personal observation in the half year following the first observations numbered about three hundred. The reports from other physicians brought the number to upward of a thousand. And the conclusion forced upon me was that certain definite and tangible results attended the administration of the extract. They were results closely similar to those that had been attained by the use of various and sundry of the biological extracts above referred to; and substantially identical with those attained by the workers at the Crocker Research Fund Institution with animal extracts, to which fuller reference will be made in another connection. But the method had merits over the antecedent ones in question in that the extract used could be readily prepared, and lacked the toxicity that characterized some of the others—for example, the bacterial extract known as Coley's fluid, the efficacy of which, in some cases of sarcoma, appears to be beyond question.

When the extract was first brought to my attention I was

told that no one had any very clear notion as to how it operated, but that it was known to contain chlorophyll, and that its action was supposed to be due either to this substance or to some unknown agent of the nature of a vitamine. It was not until about six months later that I learned the method of preparation of the extract; then the fact was revealed that it contained vegetable proteins in solution. Long before this I had freely expressed the opinion that there was nothing specific about the particular vegetable compound used to make the extract, and had predicted that it would be possible to make extracts from numberless other vegetables that would be equally effective. This prophecy was in part based on the supposition that chlorophyll was the active agent involved.

But when I learned that the extract contained vegetable proteins, a clear conception of its manner of action crystallized instantly in my mind, along the lines of force, so to speak, of the Proteomorphic theory. At once it seemed clear to me that we had to do with a protein response; that the cohorts of leucocytes and red corpuscles were stimulated into being and into renewed activities to meet a protein invasion; and that the observed action on the cancer cells was only an incidental effect due to the fact that these cells are themselves foreign proteins and, therefore, fall within the range of activities of the corpuscles. The preliminary blood studies that were already under way, the full details of which will be given presently, appeared to justify the inference. The observed facts linked with the Proteomorphic theory, in my mind at any rate, in a way absolutely convincing.

Immediately, and at a single sitting, I wrote the paper explaining the action of the remedy in the light of the Proteomorphic Theory, which was published in the *New York Medical Journal* of October 2, 1915.

I weigh my words very carefully, yet I speak entirely without hesitation, when I express the conviction that a new era in therapeutics was foreshadowed in that publication.

In speaking thus, I do not mean to refer in particular to the treatment of cancer. That, as I clearly conceived at the time, is only an incident. The subject involved is much larger. I stated this explicitly in the article in question, enunciating the opinion that a principle of protein response had been (quite by accident) invoked that would apply against all protein infections. I expressly stated the opinion that, in the attempt to explain the rationale of the action through which the vegetable proteins bring about a beneficent increase in the armies of leucocytes and erythrocites, we "gain glimpses of an entirely new field of therapeutics and shall be enabled to give at least a proximal explana-

tion of the exact manner of action of a remedy, the introduction of which, I believe, constitutes the inauguration of a method that must in future rank with serum therapy and vaccine therapy —if, indeed, it does not altogether outstrip or totally supplant both these relatively new additions to the equipment of the practical physician."

Such a view as this, if presented without both theoretical and clinical backing, must have seemed heretical. It carried the clear implication that a non-specific protein might serve as an antigen capable of decompounding proteins of many types, including the bodies of various pathogenic bacteria and various types of "malignant" cells.

The suggestion ran counter to the dominant medical thought of the moment. The familiar facts regarding diphtheria antitoxin, Wright's anti-typhoid vaccine and allied vaccines, and Ehrlich's salvarsan (to mention typical examples of three new types of medication) had revived in the mind of the profession the old hope that specific medication was to give final answer to all therapeutic problems. In the cancer field, as well as in the field of bacteriology, recent effort had nearly all been directed along the lines either of specific antigens or of remedies having elective affinity for particular cells. Various attempts to develop a cancer anti-serum; Vaughan's use of residual products of the cancer cell, and Hodenpyl's use of ascitic fluid of a cancer subject were typical illustrations of one method; and the colloidal copper treatment of Leo Loeb and selenium experiments of Ehrlich and Wassermann were illustrations of others.

It may fairly be said that most workers in the field were so thoroughly imbued with the idea of specific therapy as to cause them to look askance at any suggestion of a more general method.

Perhaps I cannot better illustrate this than by stating that among the medical men who were most closely concerned with the introduction of the vegetable extract treatment, there were those who were inclined to believe that the extract would be found to contain something having a selective affinity for cancer cells, and hence falling within the scope of specific medication. The thought of a magical "vitamine" was at least vaguely in their minds. Like the users of Dr. Gwyer's "X-substance," which produced analogous results, they were mystified by the seeming complexity of the agent empirically used. These men looked with frank scepticism on the theoretical interpretation of the action of the remedy that I presented in the paper of October 2, 1915, and did not for some time thereafter accept the view that a general principle of protein antagonism had been evoked.

It is fair to add that I myself was not prepared to demonstrate at the time when this paper was published that there might not be other agents, for example, chlorophyll, in the extract that had a share in the therapeutic action. The demonstration that the protein alone was the effective agent was the work of later months, to be narrated in a moment. But the discovery of the protein principle, and the interpretation of its action in the light of the Proteomorphic theory, was clearly revealed in this paper of October 2, 1915. My subsequent work was to elaborate and demonstrate the principle, but in no wise to change its essentials as presented at this time. There is reason to believe that the paper found a responsive audience—witness the work in non-specific protein therapy that a few months later began to attract attention in the medical journals.

Meantime I had made a statistical study of the results of the use of the vegetable extract in the treatment of cases of inoperable cancer—the only cases to which it was at first applied. The article in which I summarized the result of this study appeared in the *New York Medical Journal* of November 13, 1915. A summary of the results will be presented elsewhere. For the moment our chief concern is with the theoretical aspects of the subject rather than with the clinical details. Suffice it that the clinical experience, statistically summarized, overwhelmingly sustained the belief that the bodily response, whether or not of corpuscular origin, was of a nature to antagonize the cancer cells, and favorably to influence the general conditions of the patient, as evidenced by decrease or cessation of pain in a large proportion of cases; modification or annulment of malodor; improved appetite, sleep, and sense of well being; and, in a surprisingly large percentage of cases, actual regression of the cancer mass itself.

All these clinical changes found explanation, according to my belief, in the modified numbers and enhanced enzymic activities of the blood corpuscles, along the lines of the Proteomorphic Theory. This opinion found support in the elaborate studies of the corpuscles, in the counting chamber and on the smear, which were carried out by me personally, or under my direct supervision, in the ensuing months.

These studies of the blood were undertaken without prejudice or preconception. The earlier counts, numerical and differential, were made under my direction, to be sure, but by an assistant who had scant knowledge, or perhaps no knowledge at all, of the Proteomorphic Theory, and who made and recorded observations automatically, without attempting to classify or summarize them or to draw conclusions. When these observations were tabulated by me, they at once revealed unequivocally cer-

tain characteristic and very conspicuous modifications of the blood, comprising, in brief summary, increase of hæmoglobin, increase of the number of red corpuscles, and striking modification of the differential leucocyte count, in the direction of lessening the relative number of polynuclears, and markedly increasing the mononuclears, and in particular the large monocytes. The last-named feature appeared to link suggestively with Vaughan's observations on the enzymic activities of the large mononuclears in connection with cancer cells.

Elaborate analyses of the blood count, and of subsequent studies along these lines, are made in later sections of the present work. Here it suffices to call attention to the fact that these studies from the outset confirmed in my mind the probability that we had to do with a protein response, and that the Proteomorphic Theory supplied a key to the interpretation of the observed phenomena.

The clinical results hitherto observed were not very different from those that had been attained by various workers with different types of animal extracts, sera, and vaccines (Fichera's autolysate, Hodenpyl's ascitic fluid, Gwyer's X-substance, Coley's fluid), except that they were carried out on a more elaborate scale; but the studies of the blood in this connection were altogether new, and they constituted the determining factor in confirming in my mind the belief that the new therapeutic principle which I conceived to underlie the observed phenomena might carry us far.

It seemed to me imperative, therefore, that I should put aside other work and devote my time to the interpretation of this principle, which appeared to adumbrate vast therapeutic possibilities.

I was more urgently impelled to do so because, with enlarged experience, it became increasingly evident that the glowing anticipations of some of the earlier users of the vegetable extract in the treatment of cancer had led to bitter disappointment, in that patients who seemed at first to be on the highway to recovery reached a static period presently and then relapsed and gradually passed down the characteristic decline to the usual fatal termination.

I heard over and over the same story, from scores of medical correspondents. At first the improvement of the patient had been almost miraculous. High hopes were entertained of a recovery, although previously the case had been regarded as absolutely hopeless. But now progress was no longer cumulative; the patient perhaps remained more comfortable, with less pain, less of malodor, but there was a general physical decline; the tumor's course was no longer checked, the symptoms of

cachexia were progressive, and the end was obviously at hand. The life of the patient had undoubtedly been made more comfortable, and had almost certainly been prolonged; but the ultimate result had not been what the friends of the patient had hoped for, and what the physician had for a time allowed himself to expect.

There were exceptions to this, it is true. A few cases out of the hundreds appeared to have gone to a clinical recovery that seemed to give promise of permanency. But these exceptions, notable in themselves, were few and far between.

This, of course, was precisely the history of the various antecedent biological measures in the treatment of cancer—the experience that had led to the abandonment of most of these methods after a brief term of use. But to me the experience seemed neither unexpected nor disheartening. I had been careful to point out in my statistical reports that these were only preliminary and that the final story could not be told for months to come. I had pointed out that what was being sought was a scientific medicament and not a magician's wand. I had repudiated from the outset the suggestion that the particular vegetable extract in question had any specific qualities whatsoever that set it aside from any other extract containing non-toxic proteins.

And what was still more important—as the sequel will show—I had conceived the idea that, if the active agent involved was indeed, as I believed, a protein, as such, there could be nothing more natural than the gradual immunization of the system against the particular proteins employed, with the result that the corpuscular response would presently cease to be cumulative. This, as it seems to me, would account for the observed fact that the patient who had at first shown extraordinary response presently reached a static condition, and then entered on a period of decline.

The fact that the use of excessive dosage, or the accidental or intentional injection of the extract into a vein, with a resultant anaphylactic shock, had been observed sometimes to bring about a new period of favorable progress in a case that had reached this static phase, appeared to me to confirm the view just presented.

The essential fact, as I conceived it, now established irrefutably, was that the parenteral introduction of a protein could bring about a response that would produce such clinical modifications. The fact that the response was not indefinitely persistent, and that the ultimate clinical results fell short of the miraculous, seemed to me a detail. A very tragic detail, to be sure, for the individual patient; but by no means condemnatory

of the procedure as a whole, and assuredly not precluding the possibility of further development along similar lines.

Therefore I re-entered the laboratory (several years of my earlier professional life had been devoted to chemistry and pathology) and took up once more the routine of office practice, and the laborious but ever fascinating grind with test tube and microscope. The dominant thought was to test the protein principle as interpreted in terms of the Proteomorphic Theory. My published contention that we had to do with no specific agent, but with a general principle that could be utilized in all kinds of protein infections had found a measure of practical support in the successful treatment of a few cases of rheumatoid arthritis and one almost spectacular case of tuberculosis. The modification of the blood in these cases had been characteristic; and similar modifications were observed in patients treated with sheep serum.

My belief that the observed modifications are of the nature of a response to the introduction of a foreign protein, and not to any particular protein, had become a firm conviction. But it required further experimental support.

An obvious way to test the matter would be to produce protein extracts from a variety of non-toxic vegetable substances, and to observe their effects when used hypodermically. Such extracts were made from alfalfa seed, millet seed, rape seed, hemp seed (and subsequently from numerous other sources), carefully standardized by a nitrogen determination, and clinically tested with a variety of patients, most of whom had long been under treatment with the original protein extract, but some of whom had never previously been treated with proteins of any kind.

The vegetable proteins thus used were at first prepared by macerating the ground seeds in either salt solution or solution of sodium hydroxide. A concentration varying from two to four milligrams of nitrogen to the cubic centimeter was affected by the Kjeldahl method, and ultimately a standardization on the basis of three milligrams of nitrogen, or approximately a two per cent. protein solution, was adopted as a satisfactory and convenient compromise. Sometimes the proteins were used in the original solution; in other cases the protein was precipitated from the extract with acetic or hydrochloric acid; washed, and redissolved in a solution of sodium hydroxide. In any event, the extract was always made slightly alkaline with sodium hydroxide, the slightest degree of acidity rendering it painful on administration. I had early discovered that this was one source of irritation that made the administration of the original extract unpleasant.

Extracts thus prepared were first employed therapeutically in

July, 1916. They were tested side by side with extracts made from the conglomerate group of herbs originally employed, or from this powder with part of the original constituents eliminated. Comparative tests were continued for a period of six months, after which the original extract was entirely abandoned, the uncomplicated protein solutions made from alfalfa seed, alfalfa meal, rape seed, millet seed, hemp seed, and from egg albumin and milk albumin, used singly or in combination, having been demonstrated to produce the same clinical and blood responses, and bearing about the same relation to the original clumsy formula that a modern preparation of digitalis bears to the shot gun formula of the old woman who first used an infusion of foxglove combined with sundry inert herbs.

In a word, the validity of my early contention that the response was essentially a protein response was abundantly demonstrated.

Moreover, my expectation that a new protein would produce a new response, thus supplying means to overcome the stasis accompanying immunization to the first protein employed, was also justified in the most gratifying manner. Cases that had become static after having undergone an original period of progress, took on a new period of favorable progress on the administration of the new proteins. The very first patient to whom alfalfa protein was administered showed the influence of the new protein in a very striking way. This was a case of metastatic recurrence after excision of the cancer of the breast. The neoplasm had regressed under early treatment, but had become static, with a seeming tendency to take on new growth. It at once regressed when the alfalfa protein was administered, and presently nothing remained but a pea-sized nodule just under the skin, which was excised with local anesthesia. The patient went on to seemingly complete recovery, and at the present writing, eighteen months after the disappearance of all symptoms or appearances of abnormality, she is in robust condition and seemingly in complete health.

Theory Tested by Prophecy

It has been said that the final test of the truth of a theory is that its application shall enable one to prophesy. It is with peculiar satisfaction, then, that I make this succinct record of prophecies fulfilled. Given a therapeutic agent extracted by an unknown process from a conglomerate mixture of drugs, and showing clinical response altogether inexplicable by any known principle of therapeutics; I predicated the response—guided by the Proteomorphic Theory—as due to no ordinary pharmaceu-

tical property of any of the ingredients, but as a general response to the proteins that chanced to be extracted along with sundry inert constituents; and—still guided by the Proteomorphic Theory—I went on to predict that it would be possible to make numberless extracts having precisely comparable therapeutic action from altogether unrelated vegetable products—that, in short, any non-toxic protein would suffice, in a measure at any rate, to take the place of the proteins under observation. I predicted that it would be possible to stimulate a new response by introducing a new protein after the system had become immunized to an earlier one. I further suggested that quantitative differences would be found in the response to different proteins, in accordance with the nearness or remoteness of the individual protein, botanically speaking, to the proteins of ordinary foodstuffs.

All of these prophecies have been abundantly substantiated by experiences that now extend over a period of nearly twenty months, fortified by my personal observation of more than one hundred carefully studied cases in which clinical manifestations were constantly checked by blood examinations; and corroborated by the experience of a body of representative physicians in all parts of the United States.

Under date of December 1, 1916, I issued a Monograph of 126 pages bearing the title *The Proteal Treatment of Cancer and Allied Conditions; A Practical Study of a New Therapeutic Principle as Interpreted in the Light of the Proteomorphic Theory.* A portion of the contents of this Monograph is incorporated in the text of the present book and may there be consulted in detail. Here I wish to quote from the Foreword a few sentences that will suggest the confidence which enlarged experience had inspired—confidence which the yet wider experience of another fifteen months has abundantly fortified. On December 1, 1916, then, I felt justified in making the following emphatic estimate of results attained; which now, fifteen months later, I reiterate with no less emphasis:

"That proteals, properly administered, assuage the pain of the cancer sufferer in a large proportion of cases; neutralize malodor; stimulate the blood count and with it the manifestations of improved health and comfort; and in a conspicuous proportion of cases cause unmistakable modifications in the condition of the neoplasm itself, amounting frequently to marked regression—is scarcely more open to-day to dispute than that digitalis stabilizes the heart beat, that quinine antagonizes the plasmodium of malaria, or that mercury combats the germ of syphilis.

"There remains, however, a question as to the amount of benefit that may be expected in any individual case; and the all-

important question as to whether seeming recoveries under the proteal treatment are complete and permanent recoveries. These questions will be discussed in the ensuing pages, but with no suggestion that a final answer as to the permanency of seeming cures can be made except after the lapse of a long period of time.

"But if the question of the possible cure of cancer by the new type of medication must be left in abeyance, there is no occasion for delay in spreading broadcast the knowledge that the proteals bring a message of new hope for the cancer sufferer, whatever the form or stage of progress of his malady. The proteal remedies have already conferred unique benefits upon not far from 3,000 sufferers; they have been responsible for an enormous alleviation of pain in the aggregate, and for a notable extension of human lives.

"According to recent statistics, cancer accounts for five or six per cent. of all deaths. That is equivalent to saying that at least five million people are living in the United States to-day who must die of cancer unless medical science in the coming years deals more effectively with the malady than it has known how to do in the past.

"I dare to hope that the facts cited in this monograph justify the belief that we are beginning to see a little light in this dark field.

"I dare even to hope that the *beginning* of the end of the cancer scourge is at hand. Proteal treatment may not offer the final solution of the cancer problem; but I verily believe that it points the way to a solution.

"In any event, the proteal treatment offers to-day a hitherto unattainable measure of solace, and a message of new hope for cancer sufferers everywhere in the world."

To be able to write such an estimate, secure in the belief that the evidence already in hand abundantly justified it, might well be considered adequate reward for two years of strenuous and nerve-racking investigation. But in point of fact this was only the beginning, as I then conceived it, and as I now conceive it. In the article of October 2, 1915, in the *New York Medical Journal* I had expressly repudiated the idea that the protein response has any specific relation to cancer except in so far as the cancer mass chances to be composed of protein matter, asserting the belief that the province of protein therapy is the entire field of protein infection. I purposely refrained from mentioning bacterial infections as such, for I knew that at best the suggestion of so general a principle as that implied would tax the credulity of the profession. But that I had the bacterial infections in mind is implied in the fact that these are, as a matter of course, protein infections; and is explicitly sug-

gested in the prediction above quoted that the non-specific protein method "must in future rank with serum therapy and vaccine therapy—if, indeed, it does not altogether outstrip or totally supplant both these relatively new additions to the equipment of the practical physician."

The confidence that underlay this prediction had led me to urge the use of the non-specific protein extracts in all manner of toxæmias; and, as rapidly as opportunity offered, the matter was put to practical tests, in my own practice, and through co-operation with several hundred progressive physicians to whom proteals were supplied from my experimental laboratory. As a result, it has been demonstrated, within two years of the time when the prophecy was made, that intestinal toxæmias, anæmias, neurasthenias, rheumatoid conditions (including rheumatoid arthritis), tuberculosis, asthma, and psoriasis fall within the scope of the protein response no less than cancer, and there is no reason to suppose that even this comprehensive list of maladies exhausts the possibilities of the method.

Other Remedial Uses of the Proteals

The *Monograph*, though dealing primarily with cancer, made explicit reference to these wider and, in the aggregate, more important applications of Proteal Therapy, in part as follows:

It remains to give brief consideration to sundry conditions of the organism not characterized by the presence of malignant neoplasms, but associated with organic maladjustments that make possible the development of such neoplasms; and directly characterized by proliferation of protoplasmic tissues in my judgment comparable with cancer proper—though not commonly viewed in this light by physiologists or pathologists.

I have in mind various conditions characterized by disturbances of nutrition and assimilation that lead to abnormal growth of cells in one region or another of the body, all evidencing conditions of hyperplasia that had certain elements of "malignancy," inasmuch as they are deleterious to the organism, though varying enormously in the degree of their obnoxiousness. Among these conditions are: (1) Anæmic obesity, in which lawless adipose cells encroach on more useful tissues; (2) pernicious anæmia and the lymphæmias and myelæmias, characterized by hyperplasia of the blood-forming tissues; (3) glandular hypertrophy, as in goiter, thymus enlargement, and splenomegaly; (4) rheumatoid arthritis, characterized by hyperplasia of tissues associated with joints; (5) general arteriosclerosis, characterized by hyperplasia of the tissues of the arterial walls; (6) sundry

lipomas and fibromas of "benign" character; in addition to (7) the neoplasms commonly recognized as "malignant."

I venture to associate all these conditions, and to trace them to a common origin in maladjustments of protein metabolism, and I suggest that it might not be illogical to group them all under some such generic title as hyperproteomorphism, or the cancerous condition. I shall not attempt here to discuss even in briefest detail the interesting questions in pathology that arise in connection with the implied association of conditions of such seeming diversity. Such a discussion will form the basis of another book. Here I wish to point out very briefly two or three sets of clinical facts that give at least a measure of support to the unorthodox conception applied in this classification.

I would first call attention to the familiar fact that a well-known type of fatty and mucinous hypertrophy known as myxœdema is associated with perversions of the thyroid function; and the further fact that there is believed to be a close association between the integrity of the hormone functioning and bodily metabolism in general.

Without attempting to point out except in this general way what I conceive to be the bearing of the observation, I wish to note that it has been observed by at least one physician who was administering the mixed proteals in a case of cancer that an enlarged thyroid disappeared during the treatment.

Observations along this line have not yet reached the point of readiness for detailed publication. By way of anticipation, however, we may note that the modification of blood count under influence of the thyroid serum is singularly like that brought about by the proteals; suggesting that the action of the serum is partly explicable on the basis of its protein content. Doubtless there is also an anti-thyroid enzyme element, but the agent that causes decrease in size of the enlarged thyroid is probably not this anti-ferment, but the sheep-serum protein.

In the next instance I would note that in a case of cancer under mixed vegetable protein treatment there existed the complication of severe rheumatoid arthritis. The latter condition cleared up entirely—a seeming cure being effected under the protein treatment. This observation led to the administration of the proteals in several cases of rheumatoid arthritis uncomplicated by the presence of cancer; and the results of such treatment have been highly gratifying. In a recent case the response to rape seed protein by itself seemed as active as the response to the combined proteins.

As regards the relation of the new treatment to the form of nutritional maladjustment manifesting itself in pernicious anæ-

mia, I cannot do better than to quote a letter received not long ago from a physician in Michigan, which is self-explanatory.

"I have been using vegetable proteins in a late stage of pernicious anæmia on purely theoretical grounds. After ten injections have found an increase of over 15 per cent. in the red cells with an accompanying favorable alteration in the differential leucocyte count, and have noted nucleated red cells for the first time since the treatment was begun.

"The patient, a man over 50 years of age, carpenter by trade, is without means, having been unable to work for over 18 months. I ordered the remedy for him on my own responsibility, having become familiar with the product through using it in a supposedly hopeless case of carcinoma of the liver, secondary to gall bladder carcinoma in my wife's mother. Gall bladder and neighboring involved liver were removed and reported by pathologist at University of Michigan as carcinoma, and a hopeless prognosis given."

Vegetable protein treatment was undertaken, and continued between three and four months; after which, according to the report:

"The patient is in better flesh than ever before, is well and comfortable in every way, and the right lobe of liver, which is low, feels perfectly smooth and healthy."

It will be observed that this letter has double interest, inasmuch as it bears on the question of the value of combined proteins in the treatment of a "supposedly hopeless case of carcinoma of the liver," as well as on the question of its value in the treatment of pernicious anæmia. It is, however, only the latter point that is at the moment pertinent. I shall not elaborate the point, however, beyond stating that a letter from the same physician received several weeks later confirms the observation that the condition of this patient is benefited by the treatment. Obviously this is no more than might be expected of the administration of a remedy which has been observed in a very large number of cases to produce striking and beneficial modifications of the blood count.

A further report on the progress of this case comes to hand in a still more recent letter bearing date of October 19, 1916, telling of the resumption of the treatment after a considerable intermission.

"The pernicious anæmia case has shown a remarkable change for the better since using last package of ampules. This patient, a county case, was in a somnolent condition, and in fact had been removed from ward to private room to die. He is now bright, has lost all the general œdema, eats well, and wishes to be up and around."

Just as the physician above quoted was led "on theoretical grounds," following his observations of the results of the proteal treatment, to inquire whether the remedy might not be of value in connection with pernicious anæmia, other physicians have questioned whether its capacity to stimulate the production of corpuscular enzymes and to bring up the blood count might not make it of value in the treatment of bacterial diseases.

Very brief but specific reference to such a possibility was, indeed, made in my paper of October 2nd, in the *New York Medical Journal.* In referring to this in the *Monograph* of December 1, 1916, the suggestive comment was made that: "A limited experience in the treatment of tuberculosis appears to warrant the hope that non-toxic vegetable proteins will prove available to fortify the defensive mechanism of the body (according to the present thesis) by stimulating the corpuscular activities against the tubercle bacillus. If a non-specific protein can produce this effect, there would seem to be no reason why the same protein, or allied proteins, may not give effective aid in combating all types of pathogenic bacteria."

The above, it will be observed, is in effect a summary of the stage of development of Proteal Therapy in its wider applications, toward the close of the year 1916.

The year 1917, following the publication of the *Monograph,* saw a rapid extension of the use of Proteals. In the course of a lecture tour in the west (April 12th to August 19th, 1917), I delivered over one hundred addresses on Proteal Therapy to companies of medical men, emphasizing always the wide possibilities of the method in its application to conditions of disturbed metabolism, and specifically urging the use of the Proteals in anæmias, toxæmias, rheumatoid conditions, asthma, and tuberculosis. Partly as a result of this personal presentation, several hundred physicians have used the Proteals in these and allied conditions. More than fourteen thousand ampules of the various Proteals were sent from my laboratory to the members of the profession for such use during the year 1917 and the first two months of 1918.

A large number of these physicians have reported gratifying experiences in the use of the Proteals, notably in the treatment of anæmias, rheumatoid arthritis, asthma, and tuberculosis; corroborating in a most satisfactory way my personal experience. Some of these reports will be found incorporated in the text of the ensuing pages; which is chiefly devoted, however, to records gained in my own office, with particular emphasis on my original hematological studies. The experience of the co-operating physicians, nevertheless, forms a most enheartening background, giving assurance that the pioneer results can be

duplicated everywhere in the hands of the profession at large. The "entirely new field of therapeutics" covering the domain of "all protein infections" is no longer an unexplored territory. Proteal therapy is by way of assuming its predicted rank alongside serum therapy and vaccine therapy, and the suggestion that it may ultimately "altogether outstrip both these relatively new additions to the equipment of the practical physician" seems no longer hazardous.

If, then, making prophecy possible is the final test of the truth of a theory, the Proteomorphic theory and its corollary, the principle of the Protein Response in Therapeutics, have found abundant justification. I think I am speaking well within bounds in saying that there are few instances in the entire history of medicine in which a therapeutic method has had so secure and so thoroughly scientific a theoretical foundation. In recognition of this fact, it would perhaps be permissible to speak of the use of non-toxic (non-specific) proteins as antigens in dealing with all foreign protein invasions and inherent disturbances of protein metabolism, as utilizing and representing the "Proteomorphic Principle."

The particular application of this principle, which will chiefly claim attention in the succeeding chapter—the only application, indeed, which has been tested on an extensive scale up to the present time—has to do with the vegetable proteins, for which I have suggested, provisionally, the name of Proteals.

CHAPTER IV

THE SCIENCE AND ART OF PROTEAL THERAPY

If the testimony presented in the earlier chapters of this book is accepted as conclusive, it will be understood that the most salient bodily response to the hypodermic administration of proteins has to do with the regeneration of the blood.

I have observed, as characteristic and almost uniform effects of proteantigen treatment, increase of hæmoglobin, increase in numbers and modification in quality of the red corpuscles, and modification of the white corpuscles in the direction of normal numbers, relative decrease of polynuclears, and relative increase of mononuclears, in particular the large mononuclears, and of eosinophiles.

These modifications of the blood are too conspicuous and too uniform to be considered as accidental. They have been observed in a considerable variety of maladies, including simple anæmia, secondary anæmia, pernicious anæmia, Graves' disease, intestinal toxæmia, and other protein toxæmias, rheumatoid arthritis, chronic articular rheumatism, tuberculosis, mastitis, and cancer. The aggregate number of cases under observation is large enough to justify deductions of a somewhat definite character.

The original studies, and up to the present by far the most comprehensive ones, bearing on this subject have been made by the writer himself or under his immediate personal supervision; but corroborative testimony as to individual cases has come from many independent sources, telling of observations of physicians who have administered the proteal treatment to patients suffering from a variety of maladies. In particular these observations have had to do with the improvement in hæmoglobin and the increase of the red blood count; since a good many physicians make observation of these matters without taking time to make careful differential leucocyte count. It is hoped that physicians in general will pay more attention in the near future to the blood count in general and the leucocyte count in particular, partly, at least, as a result of the evidence presented in my cancer *Monograph* and in the present volume.

Meantime practitioners who have not facilities for careful blood examinations may observe the clinical effects of the use of the new method, which after all is, in the last analysis, the matter of genuine importance. If the patient looks better, feels better, has improved appetite and digestion, sleeps better, gains

in weight, strength and energy—practitioner and patient alike will indulge a measure of satisfaction quite independent of any microscopical findings to justify their clinical observations. Nevertheless I would urge that the most intelligent administration of protein therapy cannot be carried out without the aid of the microscope, for reasons that have been detailed in earlier chapters. This is particularly true, as I have pointed out, in the later stages of treatment. The initial doses of any Proteal may be given after a routine method, details of which will be presented more fully in a moment. But determination of dosage at a later stage of treatment, particularly in case of grave maladies, and questions as to the time when treatment may advantageously be discontinued should be answered by combining clinical observations with microscopic study of the blood. I repeat, however, that such observation is not absolutely necessary, any more than it is in connection with any other line of treatment. But my own studies lead me to feel, in common with other hematologists, that the microscope should be given a far more important place in the equipment of the general practitioner than has yet been accorded it, and I would not overlook this opportunity to reiterate that opinion.

I would urge the practitioner to carry his studies of the blood somewhat beyond the elementary stage, and I venture to make a few practical suggestions based on my own personal studies before going on to a detailed consideration of the practicalities of the administration of proteals. I am stimulated to do this partly because a large correspondence with physicians has shown a growing interest in the subject, and I feel that by presenting the matter here I can in effect answer individual inquiries as advantageously as by personal letter. What I have to say here, however, must not be taken as a comprehensive study, but only as a series of practical hints.

At the outset, I would suggest that a good deal more attention might advantageously be given to cells in the counting chamber than is commonly done. A mere numerical count does not by any means tell the entire story. It is often of interest and value to note the response of the cells to the influence of the Toisson solution that is commonly used in counting. Often cells that at first seem round, full, and normal will presently show crenated edges, shrivel in size, develop spine-like processes or fimbriations until they assume the appearance of diminutive sea urchins, and show other malformations.

It is my opinion that the time required to bring about these modifications gives at least general clues to the qualitative status of the red corpuscles; and, in particular, that the corpuscles suffering from protein toxæmia (intestinal, cancerous, or what

not) usually show an exceptional sensitiveness, their bodies becoming malformed in the course of a few minutes or a half hour even though showing normal appearance when the blood is first drawn. The proportion of cells that take on the sea urchin form should also be noted as giving a general impression of the degree of abnormality.

Sometimes it happens that under Proteal treatment the red corpuscles show a very marked betterment in size and form, so that there is notable increase in the bulk of these corpuscles in the aggregate, although the actual number may be decreased. An interesting illustration of this is shown by a case of cancer of the stomach under treatment at my office, patient No. 543. When first examined, before treatment, the blood of this patient showed 4,900,000 red corpuscles, but the great majority of these were mere fragments of normal corpuscles, distorted and misshapen, three or four of them scarcely equaling the bulk of a normal corpuscle. The hæmoglobin index was only 60, and the appearance of the patient was cachetic to the point of ghastliness. The white cells numbered 13,000.

After one week of treatment with Proteal No. 37 (chiefly proteins of mustard seed, alfalfa seed, and alfalfa meal) there was a very striking modification in the character of the red corpuscles, the dark fragments having disappeared in the main and their place being taken by corpuscles of fairly normal size and appearance. The numerical count, however, had dropped to 4,364,000. Meantime the white cells had been reduced to 8,500.

The hæmoglobin index was now 75.

At the end of the second week, 90 per cent. of the red cells were normal in size and fairly regular in contour, except that a good many were somewhat oval in shape. Many of the cells were slightly fringed at the edges, and there were a few small cells and a good many platelets. In general the red cells were recorded as presenting an utterly different aspect from the field of two weeks earlier—a tremendous advance towards normality. The total number, however, was only 4,120,000. The white cells numbered 7,200.

At the end of the third week there was farther advance in the same direction as regards the quality of cells.

At the end of the fourth week, this patient's red corpuscles showed not more than 10 per cent. of the crenated and misshapen corpuscles after standing two hours in the Toisson fluid. A large proportion of the cells were full sized and fairly normal in appearance. And the number had gone up again to 4,954,000. Meantime there had been a further decrease in the white corpuscles, which now numbers 6,130. The hæmoglobin

index had advanced week by week from the initial 60 to 70, 70 plus, and, at the end of the third week, 80. Modifications of the differential count and of the qualitative status of the white cells will be referred to in another connection. Here it suffices to say that these were of the usual character, involving increase of the large monocytes and a characteristic change in the staining quality of the cells.

It is perhaps not unimportant to add that the patient showed steady improvement in his clinical condition, as might be expected considering the blood changes. And it should be explained that the cancer involves the pyloris, closing the aperture, and that a gastro-enterostomy making an artificial exit through the anterior wall of the stomach had been performed about five months before the Proteal treatment was begun, the surgeons at that time reporting themselves unable to remove the cancerous mass, which involved not only the stomach but the liver. Since that time, prior to beginning the Proteal treatment, the patient had been given the usual variety of drugs, including iron and arsenic, together with sedatives, yet he had gone from bad to worse, suffered constantly from gastric disturbances and the regurgitation of a bitter greenish fluid. He was constantly hungry, no matter how much food he took, and had wasted away until, although more than six feet high, he weighed only 128 lbs. Could sleep little owing chiefly to discomfort in connection with the joints of his legs. The left knee joint was much swollen, and the patient limped markedly in attempting to walk.

When the patient came under my observation all drugs taken by the stomach were discontinued except that rhubarb and soda mixture was given, together with a daily dose of mineral oil to aid in regulating the bowels, which had been obstinately constipated. The patient was placed on an exclusively vegetable and milk diet, and Proteal hypodermics were administered daily in doses beginning with 3 minims and advancing pretty rapidly to a maximum of 15 minims. The response was prompt and stimulative. The patient soon handled his food better and he gained steadily in strength, presently going about by himself as he had not done for some time before. The knee joints showed quite an increase in swelling at first, but before ten days and subsided to practically normal, and the discomfort in the legs had disappeared, so that the patient was sleeping well. His complexion changed quite conspicuously, as would be expected, considering the modification in the blood, and his mental state was far more comfortable. Meantime palpation showed marked flattening of the gastric mass, which was hollowed conspicuously equatorially, and which became slightly tender on pressure, as

it had not been before. The patient mentioned also having occasionally experienced a gnawing sensation in the region of the mass, not especially disagreeable in character, but sufficient to attract attention.

I have cited details of this case because it is fairly typical. That the striking modifications of blood and the attendant clinical evidences of improvement were due directly to the administration of the vegetable protein, seems scarcely open to doubt. It is perhaps equally open to doubt whether any other treatment hiherto available could be expected to produce modifications similar in character in a late stage of carcinoma of the stomach which had brought its victim seemingly to the verge of moribundity.

In such a case as this, it may be said that observation of the blood in the counting chamber served to give corroborative evidence rather than as a guide in treatment. It should be pointed out, however, that at a later stage in such cases the microscope may give the crucial indication as to the time when it is desirable to change the character of the protein, substituting a new proteal for the one which is losing its effect. Moreover, in many cases in which the protein toxæmia is of more equivocal character—anæmias of doubtful origin, mild intestinal toxæmia, etc.—the microscope may give unequivocal evidence, through observation of the modification of the red cells above referred to, that will be of a great value in diagnosis and thereby aid in determining the probable availability of proteal treatment.

Here, for example, is a patient having tumorous masses in both breasts. Her physician has urged her to have an immediate operation for the amputation of both breasts. But examination of the blood shows only 3,200,000 red corpuscles, with extreme leukopenia, the white cells numbering but 1,800.

With such blood conditions, one could not justify an operation without preliminary Proteal treatment. The response to this treatment was immediate and extraordinary. After ten days the red corpuscles had increased to 5,716,000, and the white corpuscles to 8,400. The patient's general appearance and subjective feelings had been metamorphosed. From having been depressed and lethargic, she became exhilarated and buoyant. She declared that she felt like a girl. Presently her condition was considered suitable for an operation, and the removal of the breasts was accomplished, followed by an uneventful recovery. After leaving the hospital, however, the patient did not recover her strength rapidly. Two weeks after the operation, it was found that the red blood count was 4,516,000. This was satisfactory enough, but, on the contrary, the white count showed 16,500, obviously much too high. The Proteal treat-

ment, which had been interrupted a few days before the operation, was now resumed. Six days later the blood count showed the following: red corpuscles, 4,740,000; leucocytes, 13,500,—telling, obviously, of progress in the right direction. The hæmoglobin index had increased from 80 to 95. Clinically, there was immediate betterment associated with the resumption of the proteal treatment; the patient ceased to have fainting spells, and gained strength progressively.

It must be obvious that the microscope is an invaluable auxiliary in helping to determine the line of treatment in such a case as this. The same thing is true, as is equally obvious, of cases of anæmia of various types, and in particular of intestinal and other protein toxæmias, the clinical symptoms of which may be varied and lacking in pathognomonic character.

If we turn from the counting-chamber to the blood smear we find a further exemplification of the same principle. Here the red cells are still of interest as regards their size, form, and tendency to dry with smooth contour or with crenated edges suggestive of amœboid activity. Their tendency to take on a copper color on one hand or a bluish cast on the other in the ordinary Wright or Hastings stain (methylene blue and eosine) may indicate a condition of alkalinity or acidity as the case may be that gives at least suggestive hints as to like conditions in the patient's system. The presence or absence of a tendency to rupture, with the formation of so-called platelets, is also of interest, as suggesting the degree of pliability of the cells and the liquidity of their contents.

According to my own observations, for example, the red cells of late stage cancer subjects are of such constitution that they do not tend to disrupt and produce a normal equipment of platelets on the smear. This is consonant with the tests made some years ago at the Loomis Laboratory, which showed that the red cells of cancer subjects are more resistant to hæmolysis than normal cells. I regard the appearance of platelets in normal numbers under treatment as a favorable indication; tending at least to suggest that a modification of the chemical constitution of the cells is being made in the direction of normality.

Vacuolation of center of the red cell, indicative of paucity of hæmoglobin, and the presence or absence of normoblasts are conditions that will be observed as a matter of course. It is not always easy to interpret the precise meaning of influx of normoblasts. I have known it to occur in an individual previously in apparent health and undergoing no treatment whatever, in connection with the onset of an acute coryza that did not go on to a stage of marked infection. In the particular case that I have in mind there was, however, an accompanying jump in the

leucocyte count from 5,800 to 13,000, showing that the infection was really more significant than the clinical symptoms might have suggested. Obviously there was a marked stimulus to the blood-forming organs. An interesting feature of this case is that the presence of normoblasts and of amœboid red cells taking a coppery stain was observed two days before the onset of the symptoms of what appeared to be an incipient influenza, which, however, proved abortive.

While the observation of the red cells on the smear may thus give items of highly interesting and important information, it goes without saying that the chief interest of the smear resides in the observation of the white corpuscles. No one who has read the earlier chapters of this book needs to be told that I regard the differential count as of supreme importance. But I would emphasize the fact that a good many illuminative things are to be learned from careful observation of the leucocytes, connoting their size, form, staining qualities, tendency to agglutinate, and the like, quite without reference to the differential count, or, better stated, as supplementary to that count.

It is a not unfamiliar experience, for example, that a series of slides obtained under closely similar conditions of technique, and with the same stain, show striking modifications of the color reaction of the white corpuscles. One slide may show corpuscles that scarcely take the stain at all; a second shows the nuclei with a deep bright blue stain; a third shows corpuscular nuclei of a purplish color.

Assuming that the stain used is one of the varieties of the methylene blue and eosine combination (Hastings', for example), it may be accepted, I believe, that the cells showing the purplish nuclei are the ones that more closely approximate the normal. On the other hand, the cells that take the bright blue stain are somewhat characteristic of conditions in which there is known to be very marked disturbance of protein metabolism (for example late stage cancer), and I have come to regard them as in a measure pathognomonic of disturbed protein metabolism, however superinduced. As suggesting this condition, they are, I believe, of distinct diagnostic value.

It is natural to assume that cells that take the blue stain have an exceptionally acid quality, since they show an affinity for the basic dye. Frequently such cells show cytoplasm in which the esinophile granules of the normal cell are invisible or but very faintly revealed.

I have frequently observed that cells that show these qualities have a tendency to agglutinate or clump together. Not infrequently a smear may show the entire leucocyte population scattered into a windrow at the end, even though the red corpuscles

may be evenly distributed throughout the length of the smear. One may assume that corpuscles that show this propensity have exceptional cohesive properties, suggesting a modification of their chemical constitution. Of course the amount of pressure exerted by the spreading slide will modify the distribution of the white corpuscles under any condition, and in general it may be expected that the larger cells, notably the large monocytes and eosinophiles, will tend to be distributed farther down the smear than the average small lymphocyte. These variations must be borne in mind; but the experienced hematologist is not likely to confound modifications of distribution of the corpuscles due to changes in his technique with modifications connoting variant systemic conditions of the patient.

If there were any doubt as to this, one may satisfy oneself that the color reactions and agglutination qualities of the white corpuscles represent actual differences of systemic conditions by making a series of slides of three or four patients in succession, with three or four slides to each patient. It may then be seen that there are marked and characteristic differences distinguishing each group, lying entirely aside from the minor variations among slides from the same patient.

Not infreuently a slide that shows the blue-stain nuclei may show other white corpuscles that scarcely take the stain at all; or corpuscles of the lymphoidocyte and plasma cell order, in which the nucleus remains practically unstained while the cytoplasm takes a deep basic stain. There is, I believe, a qualitative rather than a class distinction between these two types of cells, —namely, those that take the blue stain distinctly and those that show exceedingly faint nuclei with or without basophile cytoplasm. As I interpret it, these are varying conditions of abnormal acidity of the cell, associated with a greater or less degree of activity, or a different stage of activity, in the hydrolyzing of a foreign or abnormal protein content. The fact that the cells spoken of as lymphoidocytes and plasma cells, and characterized by unstained nuclei and deep-stained cytoplasm, are in effect aberrant types of large monocytes and small lymphocytes respectively adds color to this interpretation, provided of course the Proteomorphic conception which ascribes to the mononuclear cells a chief share in dealing with foreign proteins is accepted.

Theories aside, however, the observed variations of cellular conditions, as regards staining properties, give important clues to the condition of the patient. Moreover, interesting modifications of these conditions, in a predictable direction, may be expected in connection with proteal medication.

A typical case in point is that of patient No. 543, cancer of the stomach, whose red cell count was above referred to. When

this patient's blood was examined before treatment, it is found that the leucocytes stained with very blue nuclei, many of them taking the stain very badly. Lymphoidocytes and plasma cells largely took the place of normal cells. There were no normoblasts, and no platelets. After a week of Proteal treatment, the entire character of the white cells had changed. The record reads: "Polynuclears stained beautifully, with purple nuclei; cytoplasm granular, moderately acidophile. All lymphocytes stained typically. No lymphoidocytes or plasma cells. A very normal collection of white cells, beautifully stained. Numerous big typical large monocytes. Occasional normoblasts, platelets numerous."

Two weeks later further modifications in the same direction had taken place. The white cells were evenly distributed in the smear, except that a few very large monocytes and myelocytes, owing to their bulk, dragged toward the end. Nuclei took a normal purple stain, the cytoplasm of the polynuclears conspicuously red-granuled. Platelets were now fairly abundant, and normoblasts absent or extremely rare.

It is impossible not to associate such modifications of the cells with the marked improvement in clinical symptoms manifested by the patient. When one has seen similar modifications take place under Proteal treatment again and again, the belief that there is a causal relation between the administration of the Proteals and the changed blood condition, and that the improved clinical conditions are effects and not accidental concomitants, becomes a firm conviction.

If the subject to whom the protein extract is administered is, let us say, a patient with cancer of the uterus, associated with pain, a fœtid discharge, and marked cachexia, there is likely to be a very notable modification of symptoms. The pain may largely disappear after two or three treatments; the character of the discharge may be so modified that it becomes watery and inodorous; and the general physical condition of the patient may be strikingly modified in a favorable direction. As the treatment continues, the neoplasm itself may undergo a conspicuous and unequivocal regression to a greater or less extent.

Similar modifications may be observed in malignant neoplasms of various types wherever located in the body. There remains, however, the highly interesting question as to how such changes are brought about by the hypodermic administration of small quantities of vegetable proteins.

Modifications of the Leucocyte Count

A further clue to the answer is found in the fact that conspicuous modifications of the leucocyte count no less than of the

red cell count almost invariably follow the administration of the proteins. These changes are of a kind susceptible of interpretation in terms of the Proteomorphic theory. But they have a high degree of interest quite aside from theoretical interpretations. As gauged by the study of about 200 original cases, they appear to include a tendency to bring the polynuclear leucocytes and small lymphocytes towards the normal; whereas the basophiles and eosinophiles are markedly increased, and the large monocytes are increased by several hundred per cent.

Before giving details as to these interesting modifications of the blood count brought about by the administration of protein antigens, I would again call attention to the highly interesting laboratory experiments reported by Drs. M. W. Manwaring and Yoshio Kusama, of the department of bacteriology and immunity of Leland Stanford, Jr., University, as recorded in the *Proceedings* of the Society for Experimental Biology and Medicine, of May 24, 1916. These experiments go to show that the blood corpuscles of a rabbit actively absorb goat serum protein, whether the goat serum is mixed with the (defibrinated) rabbit's blood in a receptacle outside the body or whether it is injected into the system of the living rabbit.

This observation, obviously, gives strong support to the assumption of the Proteomorphic theory that the blood corpuscles are the chief agents concerned in dealing with foreign proteins —the assumption that forms the chief basis for the explanation of the therapeutic action of the protein remedies with which the present book is concerned.

In attempting to interpret the meaning of the observed changes in the blood picture, however, one is entering quite unexplored territory, and a territory in which the newly observed facts do not at all times serve as an accurate guide.

Interesting hints as to the mutual relations of the various types of white corpuscles are given by charts in which the different groups of cells are represented by graphic lines (see the cancer *Monograph*). It is hoped that the study of these in connection with the protein remedies will throw new light on the obscure relations of the different types of leucocytes. When a much larger series of charts is available than at present, it is certainly to be expected that relations will be observed between the mutual rise and fall of the different types of corpuscles under treatment that will help to explain the genetic relations of these bodies.

In making such charts, it is desirable to transform percentages of the differential leucocyte count to actual numbers. When this is done, one is impressed with the general observation that there seems a strong tendency, under the Proteal treatment, for the polynuclear leucocytes and the small lymphocytes to be modified

in number so that, after treatment has been continued for a time, they fall within normal limits. Here, for example, is one chart (Case No. 332) in which at the outset the number of neutrophiles was 5,328, and the number of small lymphocytes 2,131; these numbers representing in each case an excess above the maximum normal limits, as usually computed. But after treatment had extended over about 90 days, it was observed that the polynuclears numbered 4,356, and the small lymphocytes 1,824; both these numbers representing a (high) normal count.

But in the meantime, it should be noted that the large monocytes, which at the outset numbered 1,420, had increased to 2,403. The original count is far in excess of the normal (which seldom exceeds 400), and the final count exceeds the maximum normal limits by 600 per cent. The assumption is, according to the present thesis, that before treatment the large monocytes had been stimulated to excessive production under influence of the disintegrated cancer cells; and that the protein treatment effected a further stimulation.

A similar proportionate increase in the eosinophiles has taken place, there being none noted at all before treatment and the number having risen almost continuously until 356 were noted at the later count,—about double the normal maximum limit.

Whatever the interpretation put upon these facts, it would appear, as already pointed out, that such a super-normal count of large monocytes and eosinophiles constitutes a favorable condition in the organism associated with improved general health of the patient and a tendency to combat the cancer cells effectively. Indeed, I never feel that the desired results are being attained unless this characteristic response is observed.

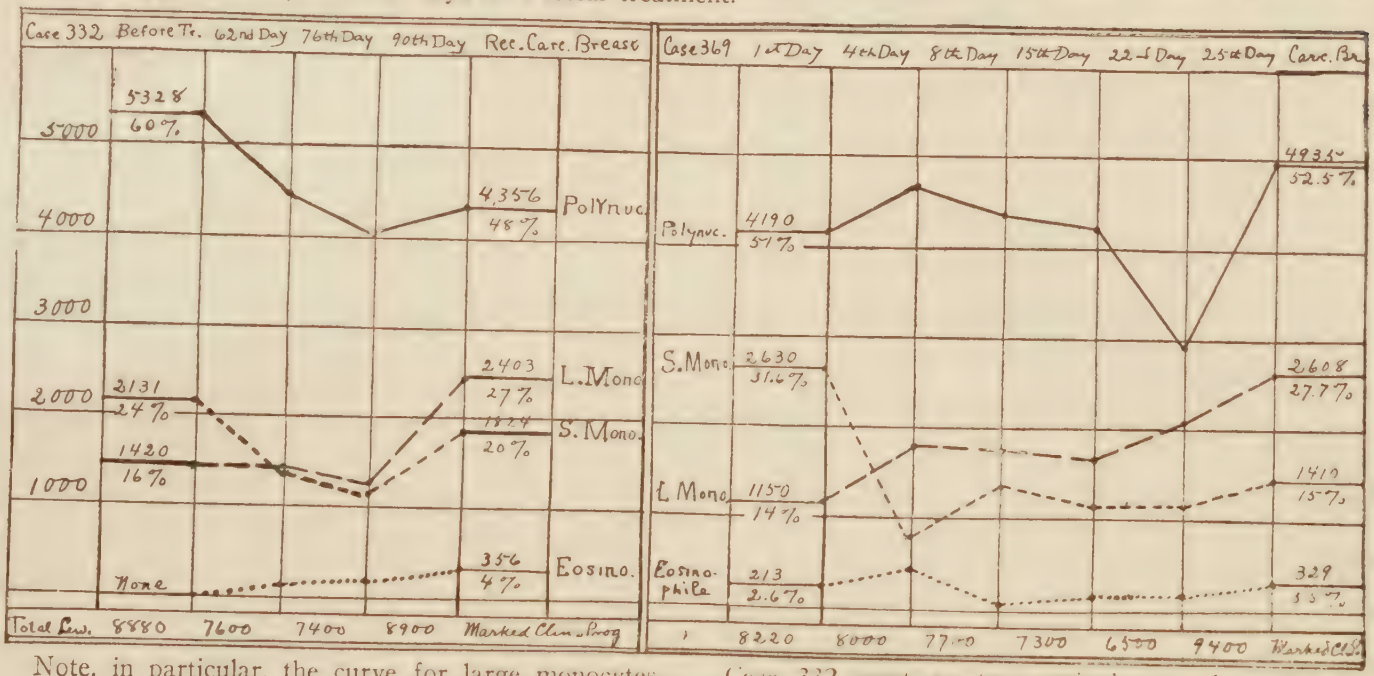
Another chart illustrates the same principle in a different way; inasmuch as it was necessary to increase the number of neutrophiles in order to bring them to a high normal limit. It will be observed in this chart (Case No. 369) that at the outset the neutrophiles numbered 4,190 and the small lymphocytes 2,630. At the end of three weeks' treatment, the polynuclears had risen to 4,935, and the small lymphocytes had dropped to 1,410. Here, as before, the final count shows polynuclears and small lymphocytes within normal limits.

In the meantime, in this second chart, as in the first, the large monocytes have risen conspicuously; in this case from 1,150 to 2,608; and the eosinophiles have increased from 213 to 329. The numbers here are substantially in accord with those shown in the other chart. Such close agreement is a matter of coincidence, although the same general principle will be seen reiterated in a large number of cases.

A striking feature of both these charts is the marked modifi-

Chart 1—Original Cases

The differential leucocyte count in two cases of Carcinoma of the Breast (Case 369 a Male) during periods, respectively, of 90 days and 25 days of Proteal treatment.



Note, in particular, the curve for large monocytes.

Both cases showed marked clinical progress during the above periods.

Case 369 subsequently developed a spinal complication and died.

Case 332 went on to seemingly complete clinical recovery, and at the time of preparation of this chart she is still in robust health; a period of fifteen months having elapsed since her recurrent carcinoma was pronounced inoperable and she began Proteal treatment. Full history of the case is given in another connection.

cation in the number of neutrophiles and small lymphocytes from the initial dose of the vegetable protein. A question not unnaturally arises as to whether there is any mutual relation between the two groups of leucocytes, or whether the modification of their numbers has been brought about independently. Glancing at the first chart, one might think that there must be some mutual relation, inasmuch as the lines showing modification of the neutrophiles run almost parallel with those showing modification of the small lymphocytes. But in the second chart, we find that the slope of the line is reversed, the neutrophiles showing a rapid rise after the first dose and the lymphocytes a rapid decline.

It is not impossible to frame a theory that would harmonize these seemingly contradictory results, but perhaps it is not worth while to attempt to do so at the moment. Our chief present concern is with the observed facts, which fortunately are unequivocal. As above outlined, these include a notable departure from the normal blood picture brought about by the administration of the protein remedies as evidenced in a relatively enormous increase of the larger monocytes, a conspicuous increase of the eosinophiles and basophiles; and a tendency to bring the small lymphocytes and the neutrophiles within normal bounds.

By way of recapitulation, it is well to recall that Vaughan's experiment seems to show that the specific enzymes of the large mononuclears have particular value in proteolyzing the cancer proteins. Stated otherwise, the large mononuclears would seem to have particular affinity for cancer proteins; which is only another way of saying, probably, that they are particularly adapted to deal with proteins of an embryonic type. The fact that the large mononuclears abound relatively in the normal blood of the child may be recalled in this connection.

Blood Changes in Tuberculosis

Many instances of spectacular changes in the corpuscular relations under Proteal treatment are given in the cancer *Monograph*. Here it is desirable to supplement these records by citing a few cases representing maladies of different types.

Here, for example, is the case of J. G., a patient in the late stages of tuberculosis of the lungs. Left lung solidified. General condition extremely cachectic, so emaciated and frail that his tenure of life seemed very uncertain. His blood showed 3,260,000 red corpuscles of exceedingly poor quality,—variant in size, malformed in shape. The white corpuscles numbered 14,500, of which 87 per cent. were polynuclears, 7.3 per cent. small lymphocytes (including plasma cells), and 5.6 per cent. large mononuclears. The polynuclears are recorded as of red-

purple nuclei, not sharply defined from the cytoplasm, which was opalescent, and distinctly reddish. The large monocytes were typical, dark, with opaque cytoplasm.

This patient was not treated in my office, but by an associated physician, and a second blood count was not made for six weeks, at which time the red corpuscles had risen to 4,395,000 in number and the white corpuscles had come down to 12,500, of which 78.3 per cent. were polynuclears, 7.3 per cent. small lymphocytes (no plasma cells), and 14.3 per cent. large monocytes. The red cells in addition to their spectacular increase in number were much more normal in appearance. A good many platelets had appeared, and free microblasts, often large, of which there had been none at the earlier period. The polynuclears were very acidophile and granular, with full cytoplasm. There was extreme progression to the left in the Arneth sense—that is to say a very large number of single-nucleated neutrophiles. The large monocytes were large and fairly typical; the cytoplasm dark, but clearly differentiated from the nucleus. The number of these large monocytes had increased, as will be observed, by 250 per cent. The change in size and quality was not less conspicuous.

A fairly plausible interpretation of these microscopical findings, and one consonant with the clinical history and the known pathology of such cases, would be that there was marked bacterial infection (indicated by the leucocytosis, with conspicuous preponderance of polynuclears), but that there was also marked general protein infection, comparable to the infection from cancer, the solidified lung mass having many of the characteristics of a malignant neoplasm. The response to proteal treatment, indicated by increase of red corpuscles, decrease of white, decrease of the polynuclear preponderance, and marked increase of large monocytes may be taken as suggesting interesting possibilities of proteal treatment for tubercular cases even at a late stage of unfavorable development.

In another late-stage case of pulmonary tuberculosis the red corpuscles before the administration of Proteals numbered only 3,964,000, and were of such quality (90 per cent. diminutive and misshapen) that their functional efficiency must have been far more than proportionately reduced. After seventeen days of Proteal treatment (doses of 3 to 7 minims of Nos. 37 and 45), the red cells were metamorphosed in character, and increased in number to 4,500,000. Clinically there was striking improvement. Temperature and pulse reduced to normal (from 101 and 115, respectively); cough much less; better appetite and sleep; strength and sense of well being so greatly improved that the patient asked to be allowed to go back to work. Prior to beginning treatment her physician had told her that she had but

one chance in a thousand to live, and that chance conditioned on her going at once to the mountains. Nine months later this patient seemed clinically well, and the blood record was: Hæmoglobin 85; red corpuscles, 5,165,000; white corpuscles, 5,500,—an absolutely satisfactory numerical count.

Tuberculosis and Protein Poisoning

It is my personal view that an advanced case of pulmonary tuberculosis represents a condition in which the chief menace is not from toxins directly developed by the tubercle bacillus itself, but from toxins generated by mixed infections plus the toxic products of partial proteolysis of the tissues making up the lung mass.

Stated otherwise, I regard a tubercular mass as a foreign growth which may have the same effect on the blood, the blood-forming organs, and the organism at large as the types of foreign growths that we term malignant neoplasms. The tuberculosis patient, like the cancer patient, dies ultimately either of hemorrhage or of protein poisoning. In the latter case (and this may be said to represent the normal progress of pathological events, if the phrase be permitted), the same kind of strain is put upon the blood-forming organs, and the same disturbances of the blood cells are brought about in tuberculosis and in cancer. Clinically, the cachexia of the late stage tuberculosis patient and that of the late stage cancer patient cannot be distinguished one from the other. I have seen two patients side by side, both cachetic to the verge of moribundity, one having a solidified lung and the other a carcinoma of the stomach, yet so closely similar in general appearance that even a practiced eye could not determine which patient had the injured lung and which the injured stomach. What could be determined at a glance was that both patients manifested profound disturbances of metabolism, characterized by lack of good red blood. Both of them have blood-forming organs that have overworked against persistent protein invasion until they have reached the stage of sheer exhaustion.

Under the microscope, the blood of these two patients may be as similar in its abnormalities (decrease of red corpuscles, increase of white, preponderance of polynuclears, qualitative modifications) as their clinical manifestations of malnutrition are similar.

When we consider the matter in this light, it no longer seems strange that administration of the same treatment to these two patients may be beneficial to both. A few drops of Proteal from the same ampule may be administered hypodermically in succession to the tubercular and cancerous patients respectively day by

day; and it may fairly be asserted that each will give evidence, both clinical and hematological, of an organic response that is definite and highly gratifying.

As to what will be the ultimate extent of such response, no predictions can be made in any individual case. It is axiomatic to say that everything depends upon the degree of involvement of tissues, both local and general; the inherent vitality of the patient; and the responsive capacities of the blood-forming mechanism. These are matters regarding which no two patients will be precisely alike, and regarding which the physician cannot always form an accurate estimate. In particular, that intangible but highly important thing which we call inherent vitality may come to the rescue of many a patient whose case seemed hopeless; whereas another patient whose state seemed less desperate may not have quite the same recuperative qualities of cellular tissue. The wise physician will always hold prognosis in abeyance and watch for results before forming an opinion in his own mind as to the outcome.

I would call attention to what I have said in the cancer *Monograph* as to the absurdity of hoping to restore cells that are actually degenerated, reiterating that this can no more be expected when these cells are part of the liver or pancreas or lung than when they are part of an amputated arm or leg. But I would also repeat that we can seldom feel certain as to the amount of involvement of tissue in any given case where an internal organ is involved; and, secondly, that a comparatively small portion of remaining normal tissue may sometimes show surprising capacity to take on itself functions of the entire organ. A familiar case illustrating the latter point is the well-known capacity of one kidney to do the work of both.

Questions of ultimate prognosis aside, however, we are justified by present experience in expecting that, in a very large proportion of cases of the kind just cited (late stage tuberculosis and cancer), as well as in a variety of other conditions of disturbed protein metabolism that have led to anæmic and cachetic conditions, the exhibition of Proteals will produce at least a temporary response of the blood-forming organs that will be manifested in marked modification of the blood count and in more or less conspicuous clinical improvement of the patient.

I think I am speaking within bounds when I say that my experience justifies the conclusion that the Proteals, thus administered, have such powers of stimulating the blood-forming mechanism as to place them in a class quite by themselves among tonic remedies. I have much confidence that the future will justify my present belief that this form of medication is destined

to make the old, familiar tonic remedies—notably iron and arsenic—in their old method of administration, obsolete.

In making this suggestion, I would not have it understood that I expect to see iron, arsenic, and other old friends of this category disappear at once from the armamentarium of the physician. Proteal remedies will not altogether displace these old friends any more than salvarsan has altogether displaced mercury. It is not to be expected that any one type of medication will be applicable to any and every type of case, even where there are seemingly similar maladjustments of functioning. Yet I reaffirm the conviction that present experience justifies the belief that the tonic remedies that have been almost the sole reliance of the physician in anæmias associated with disturbed protein metabolism (and hence associated with most of the disorders of middle life and old age) are rendered obsolescent by the advent of the new method.

I am aware that such an opinion must seem heretical, perhaps even fanatical. Yet I express and reaffirm it calmly and with confidence based on the observation of a series of cases large enough, and varied enough, in my opinion, to be dependable.

It will be understood that the opinion just expressed is based on personal, first-hand observation both clinical and microscopical. The work with which we are dealing is pioneer work. So far as I am aware, no one but myself and my immediate associates have hitherto dealt extensively with non-specific vegetable proteins as such, either in laboratory or clinic, as therapeutic agents for hypodermic administration. It is true that several thousand physicians have administered the original proteal extract, and I have profited by their clinical experience; but for the most part the physicians have administered the remedy empirically in accordance with my directions, and comparatively few of them have watched the blood count. Those who have done so, however, have reported observations, confirming in the most substantial manner the original studies with which the present volume is largely concerned.

Here, for example, is a letter that chances to come to hand the morning of the present writing, from a prominent physician in a neighboring city who says:

"I have now used the Proteal No. 37 for twelve days and have reached the dose of 15 minims without any local or general reaction. I have increased the dose to 17 minims and will of course watch for reaction. The only constitutional change thus far has been a true increase in the mononuclear leucocytes with a decrease of the small lymphocytes; also an increase in the red blood cell count."

A pioneer in any line of research work must always await with interest corroboration of his results by other workers. Naturally I shall be pleased to have reports at all times from candid observers, whether by way of corroboration or criticism; but I repeat that the evidence already in hand, based on my personal observation, is so comprehensive, so unequivocal, and so convincing that I await the ultimate verdict of the profession with absolute confidence.

All this, however, is in effect a digression. Let us again take up briefly the interpretation of the blood changes that are brought about by Proteal medication, in so far as they are of practical interest and importance to the practitioner; following with some explicit hints as to the practical administration of the new method in cases of malnutrition of sundry types, from simple anæmias to the profound cachexia of tuberculosis and carcinoma.

An Interpretation of Corpuscular Action

As regards a somewhat more detailed interpretation of the blood count, and in particular the differential count, there are certain opinions that I hold provisionally, regarding which more elaborate publication will be made elsewhere, to which brief attention may be given. As elsewhere pointed out, this subject is one in which very little work has been done, and regarding which the opinions of the pathologists are altogether vague. So far as I know, the question has not hitherto been asked, let alone answered, as to why in normal blood the polynuclears number 60 to 70 per cent. of the total leucocytes, the lymphocytes 20 to 25 per cent., and the large monocytes and eosinophiles and basophiles make up a relatively insignificant population. Yet there must be reasons why there is this distribution of corpuscles in normal blood; reasons associated with the variant functions of the different types of cells.

In attempting to interpret the observed blood changes under Proteal treatment, peculiar difficulties are encountered in the fact that the physiological activities of the corpuscles have been but vaguely understood.

Ordinarily, the pathologist is guided in the interpretation of what he sees by known physiological laws. The student of microscopic pathology has for guide the well-recognized findings of the histologist. But in the present instance such aid is not available. We have, to be sure, records as to the relative numbers of different types of blood corpuscles in health and acute infections. The further fact is available that the polynuclears appear to be especially concerned in the direct battle against invading bacteria. But with that antecedent knowledge practi-

cally ends. If one asks, for example, why basophiles, eosinophiles, and large monocytes are few, whereas small lymphocytes are relatively numerous, and polynuclears still more so, no answer has hitherto been forthcoming.

It is axiomatic to say that such distribution of numbers must be consonant with the needs of the average body and with specific functions of the different types of leucocytes; but as to the nature of these needs and the character of the function there is entire silence on the part of physiologists and pathologists alike.

In the first exposition of the Proteomorphic theory, I put forward the suggestion that the leucocytes as a class have for their broad general function the hydrolysis of proteins and the earlier products of protein decompounding. To the mononuclear cells in particular I ascribed the function of dealing with the full-sized protein molecule. It was further noted that the large monocytes appear to have a peculiar relation to the decompounding of such neoplastic cells as those of cancer, and I ventured the suggestion that the small lymphocyte has to do with the catabolism of normal serum proteins, in rendering them available for bodily use. But beyond this no detailed interpretation of the functions of the different leucocytes was attempted.

In the three and a half years that have elapsed since the Proteomorphic theory was conceived and exposited, I have devoted a large share of my time to studies that brought me directly in contact with problems of corpuscular activity in disease and in health. During a considerable part of this time I have devoted several hours of each day to the microscopic study of blood corpuscles in counting-chamber and on stained smear. While chiefly concerned with the blood of persons suffering from maladies of disturbed metabolism, and in particular with modifications of blood under protein treatment, I have checked these observations with studies of normal blood under various conditions.

This is not the place to give detailed account of these studies, which, indeed, have not yet reached the stage where final analysis is desirable. But, by way of preliminary report of matters hitherto unpublished, it may be worth while to give a brief outline of a theory of corpuscular action that seems to be at least worth considering as a working hypothesis, although confessedly subject to modification in the light of future evidence. This hypothesis is only one of numerous suggestions that present themselves, and which at various times have been entertained in the course of my investigation. I hold it and put it forward not in the least dogmatically or as having finality, but in the thought that it may serve a useful purpose in guiding the investigations of others,—and I assume that the present publication,

because of the hematological facts already presented, will stimulate a large number of investigators to take up the study of the blood with new zest and from new angles.

The working hypothesis which I now suggest hinges on an assumption that is almost absurdly simple—which may or may not be a merit. The suggestion is this—that the different groups of leucocytes, in the order of their numerical abundance, deal primarily with the successive groups of protein decomposition products in the order of their numerical molecular representation. That is to say, the least abundant group of leucocytes (namely the large mononuclears and binuclears) deal with full-sized protein molecules; the next larger group of leucocytes (namely the small lymphocytes) deal with molecules of the proteose or albuminose order; the third and most abundant group of leucocytes (namely the polynuclears or neutrophiles) dealing with protein-product molecules of the peptone order;—it being understood that the extremely abundant red corpuscles take up the work of decompounding at the polypeptid stage and complete the final disintegration into amino acids and toxic by-products, such as uric acid, urea, and creatinine.

It will be recalled, as giving a sort of apriori plausibility to the assumption, that the numerical relations between the normal numbers of different types of leucocytes are, in general terms, the same as the numerical relations between the numbers of molecules in the different orders of protein products. This relation of course does not hold when the red corpuscles are under consideration, since these are many times more numerous. But this seeming inconsistency is explicable on the plausible assumption that large quantities of molecules of the polypeptid order enter the circulation normally, through the intestinal wall. Indeed, it has been suggested that the red corpuscles may be called upon under normal conditions to complete the hydrolysis of the polypeptids wholly or in part, the question as to the precise condition in which the protein product normally enters the circulation not being clearly settled.

Even though the enteric enzymes normally reduce the polypeptids to the amino-acid stage, it must happen very generally that they fail to some extent of their complete function, permitting the entrance of a greater or less number of polypeptid molecules. The same thing is true, of course, of a certain number of large molecules, including the full-sized protein molecule itself; but the entrance of the latter must be relatively infrequent,— a fact that in itself accounts, we may suppose, for the relative paucity of large mononuclears in normal blood.

It will be observed that in the above summary, reference is made to a group comprising mononuclears and binuclears. The

latter term of course connotes eosinophiles and basophiles. Very little has been said in recent pages about these two types of leucocytes, beyond noting that they tend to increase under proteal treatment just as do the large monocytes. I have long been disposed to regard the eosinophiles and basophiles as cells of the same order, representing either stages of individual development or modified condition of chemical composition (say acidity versus alkalinity), in effect no more variant than different specimens of polynuclear leucocytes some of which show clear unstained cytoplasm while others are markedly granular and acidophile.

I am by no means certain that basophiles and eosinophiles are not to be regarded as matured stages of large monocyte development. It is at least within the possibility that a monocyte that has ingested a certain amount of protein and transformed it, let us say, into proteose may divide its nucleus and have its enlarged cytoplasm just prior to disruption assume a condition that modifies its staining qualities so that its appearance is greatly modified. On this assumption, the relative scarcity of eosinophiles and basophiles would be explicable on the ground of their relative shortness of individual life, it being assumed that the incidence of the granular condition presages disruption.

It may be recalled in this connection that the Russian investigators Avrowrow and Timofeeosky have suggested that eosinophiles are only monocytes that have ingested red blood corpuscles.

No doubt many objections could be urged against this linking of the large monocyte and the eosinophile and basophile as members of the same series. I am not aware, however, of any objection that seems insuperable. Meantime the observed coincidence between increase of large monocytes and increase of eosinophile and basophiles under proteal treatment (see numerous tables in the *Monograph*), is at least not inconsistent with the assumption.

It is consonant with what we know of the mutual relations of bodily organs to assume that, even if the above interpretation of the primary action of different types of leucocytes be accepted, it does not follow that any type of leucocyte is absolutely restricted in its possible activities to the hydrolyzing of protein products of a particular size. I have already suggested that the stage of decompounding to which a protein molecule may be subjected within the leucocyte may depend to some extent on the amount of pabulum ingested, which in turn would be a function of the abundance of leucocytes on one hand and of protein products in the blood on the other.

To illustrate my meaning, we might assume that, granted a

given prevalence of full-sized protein molecules, when the large mononuclears are few, they would individually secure large increments of pabulum, and would on the average be disrupted when this pabulum has reached the proteose stage, thus necessitating a full equipment of small lymphocytes to take up the work of hydrolyses. On the other hand, if without increase of protein pabulum, the number of large monocytes is increased, we may assume that on the average they would carry the work of decompounding to a lower stage, possibly even to the peptone stage, and hence be able to turn their product over directly to the neutrophiles, thus to some extent rendering the presence of small lymphocytes superfluous. Some blood charts have been presented which seem to give plausibility to this suggested complementary relation between the activities of the large and small monocytes.

Applying the same line of reasoning to other types of leucocytes, we may assume that under exceptional circumstances, the small lymphocyte may be able to deal with the full-sized protein molecule on one hand and to bring it to something approaching the polypeptid stage on the other hand; thus supplementing the functions of large monocytes and of polynuclears. Cases of lymphatic leukæmia suggest this possibility. Meantime the polynuclear itself, although ordinarily concerned with transforming peptones into polypeptids may conceivably on occasion deal with proteose on one hand and carry the polypeptids toward the amino-acid stage on the other. A certain complementary relation observable between the mononuclears, as a group, and the polynuclears, in the charts before referred to, may perhaps thus be explained. That a full red-cell equipment minimizes to some extent the need of the services of polynuclears is also at least a tenable hypothesis.

I have under treatment a patient who for months has maintained a clinical status of fairly robust health with a red-cell equipment of from 2,176,000 to 3,909,000, and a leucocyte count (chiefly small lymphocytes) ranging from 680,000 to 1,412,000. On the smear, the small lymphocytes are like bunches of grapes; large mononuclears with obscure nuclei are abundant; but polynuclears are hard to find. Here it is impossible to avoid the inference that the small lymphocytes perform functions normally reserved for polynuclears on one hand and erythrocytes on the other. This interesting case of lymphatic leukæmia will be discussed in greater detail elsewhere.

It is probable that another factor that may disturb the mutual relations of the white corpuscles is to be found in the relative amount of fat to be dealt with in any organism. I have suggested that the polynuclears may have a share in dealing with

the metamorphosis of fats; but it is consistent with the above line of reasoning to assume that the lymphocytes also may have a hand in this work. Possibly the relative shares of the two types of leucocytes in dealing with fats may vary indefinitely under diversified conditions.

A further word must be said about the relation of the various leucocytes to the type of protein represented in the bodies of bacteria. At first glance it may seem that the observed fact that polynuclears deal with bacteria, ingesting them bodily, is inconsistent with the assumption that the chief work of the polynuclears is to deal with the partially decompounded protein molecule. As to this, however, it will be recalled that the suggestion was made that the so-called "opsonins," the presence of which was found by Wright to determine the activities of the leucocytes as ingesters of bacteria, may be enzymes secreted by the mononuclear leucocytes; but it is perhaps even more important to recall that the proteins of bacteria are probably very different in quality from the proteins of vegetable and animal tissues in general.

Reference has already been made to the fact that the encasement of the bacteria is of a fatty or lipoid character. It has been pointed out by Leathes that it is not the cell-membrane alone of the bacteria that is so constituted, but that the fats enter into its entire structure. He says: "These fatty substances, which form a considerable part of the bodies of tubercle bacilli, not only exhibit a very low iodine value, but offer remarkable resistance to measures that are commonly efficacious in saponifying fats. And there are reasons for thinking that the vitality and power of resistance of such organisms is intimately dependent upon the properties of the fat in which their bodies are enclosed or with which they are impregnated."

In dealing with the bodies of pathogenic bacteria, then, the organism is not contending at all exclusively with foreign proteins, but with structures in which the protein basis is so incorporated with fatty matter as to modify the conditions very markedly. Moreover, it is probable that the bacterial protein itself is of a quite different order from the proteins of true plants and of animals. The low plane occupied by bacteria in the organic scale suggests the probability that the bacterial proteins have molecules of a relatively simple order, comparable perhaps in their complexity to peptones or proteoses rather than to true proteins. On this assumption, as well as in consideration of the presence of the fat, the recognized capacity of the polynuclears to deal with bacteria is entirely consistent with the function ascribed to these leucocytes in the above provisional hypothesis. The instances of observed incapacity of the large

monocytes to deal with bacteria find further explanation in the assumption that the bacterial proteins are of a low order of molecule structure.

Incidentally, this line of reasoning makes it clear that we are not to expect the same increase in large monocytes from the use of bacterial proteins as proteantigens that may be expected from the use of vegetable or animal proteins. The observed polynucleosis from the injection of bacterial products is quite what might be expected.

It may be added that if the above hypothesis is valid as to the assumption that the large monocyte is chiefly concerned with the full-sized protein molecule, we should not expect so pronounced a large monocytosis from the injection of, for example, peptones as from the use of the full-sized protein molecule or molecules of the proteose order. Practical observation of the relative response to proteins, proteoses, and peptones, used as antigens, when carried out on an adequate scale, will go far toward testing the validity of the above assumption as to the specific functions of different types of leucocytes. Experiments directed toward this end are already under way. Comparative studies are being made, for example, of blood charts in cases treated with the unbroken protein molecule as compared with cases treated with the newer Proteals, containing proteoses and peptones.

A tentative analysis of these tables tends to give a certain amount of support to the above thesis, inasmuch as the response to the partially hydrolyzed proteins appears to include the polynuclears more markedly and the eosinophiles and basophiles less markedly than the response to the unbroken molecule. The evidence, however, is not yet sufficiently extensive to be demonstrative, as only a small part of the material in hand has been analyzed. Pending the results of such analysis, it will be well to bear in mind the fact that the generalization as to the protein blood response enunciated in the first edition of the cancer *Monograph* and throughout the earlier chapters of this book refer to the unbroken protein molecule.

Meantime the series of tables and charts already in hand, showing the corpuscular response to the administration of proteantigens for the most part representing the full-sized molecule, appear to establish the broader outlines of the Proteomorphic theory as to the manner of handling of foreign proteins in the parenteral system beyond cavil. No one who studies these tables even casually is likely to question, I take it, that the proteantigen response is directly and strikingly concerned with the blood-forming organs, and that increase of large mononuclear

leucocytes on one hand and of red corpuscles on the other are critical features of that response.

That the characteristic response may be kept up for many months is adequately demonstrated in tables above presented. The efficacy of substituting new proteins when the systemic response has flagged has been amply proved. Whether there are any limits to such substitution, and to what extent it is desirable to keep up the proteantigen treatment after the seeming recovery of a patient, are questions for the future to decide. It would appear that the study of the blood in a large series of cases must furnish the best clues to an answer.

Age and the Blood Count

In attempting to account for the observed facts of corpuscular variation between childhood and adult life, I have been led to question whether the salient fact that the polynuclear count increases from about 40 to 60 or 70 per cent. of the total leucocyte count with the advance in years from adolescence to adult life, may not be merely an evidence of response on the part of the organism to the perpetual bacterial bombardment to which it is subjected. It is familiarly known that bacterial products make up a significant part of the normal fæces; and, in general, it is understood that we are perpetually assailed by bacteria which have become relatively innocuous merely because of their universal prevalence.

Obviously, in the natural course of events, such infection must become cumulative; that is to say, we must suppose that on the average the adult individual is more comprehensively affected than the average child. On the hypothesis put forward in an earlier section, it would be the middle products of protein decompounding chiefly in excess. Conceivably this may be the reason why the polynuclear count goes up, reaching in adult life very frequently a status of approximately double that of the average of childhood and adolescence.

If this interpretation be correct, the so-called normal leucocyte count of adult life might be said to be in itself a manifestation of abnormality. Such a statement sounds paradoxical, but it may connote an important truth. It is a suggestive fact that in a patient long subjected to Proteal treatment associated with careful attention to hygiene of diet and digestion, it is observed that the polynuclear count very generally comes down as the patient improves, and may even be reduced to the standard of childhood—40 per cent. or thereabouts. In two or three instances where the patient had been for many months under

proteal treatment, I have recorded a polynuclear count of only 39 per cent.

It seems not altogether unlikely that the relatively low polynuclear count of childhood accounts for the susceptibility of the child to the familiar exanthemata; and that, contrariwise, the abundance of polynuclears in the adult organism accounts for the relative immunity of adults to these diseases. It would appear to be a case where the fighting equipment of the body, as directed against bacteria in general, has been brought to a stage of preparedness in the average adult that makes it possible to attack and overwhelm the germs of, for example, measles and whooping cough, whereas the same germs would have been able to make effective entry into the system of the average child.

A similar line of reasoning may perhaps be applied to account for the observed fact that the red corpuscles are less abundant in the blood of the child and adolescence than in the blood of the average adult. Incidentally, this fact in itself would appear to prove that the red corpuscles have some function other than the carrying of oxygen, inasmuch as the cellular activities of childhood and adolescence must certainly be somewhat more than on a par with those of the adult. Accepting the Proteomorphic interpretation of the function of the red corpuscles as the agents concerned in dealing with the end products of protein metabolism, the increase of these corpuscles in adult life might be interpreted as showing an increased protein infection of a character to charge the blood with larger quantities of end products (of the polypeptid order) with advancing years, associated perhaps with waning power of the digestive apparatus.

The fact that physiologists commonly mention 4,500,000 red corpuscles as the average normal increment for women and 5,000,000 as the increment for men—a fact hitherto, so far as I know, entirely unexplained—may conceivably be accounted for on the supposition that men, on the average, eat larger quantities of protein food than women. The proverbially daintier appetites of the female sex accord with this hypothesis; which is here put forward, however, only as a suggestion. The greater activity of the male would be an obvious explanation from a more conventional angle; but comparative histology robs this explanation of force by reminding us that relatively inactive animals like the sheep have a high erythrocyte count, whereas excessively active birds have a low count.

Meantime my personal studies leave me very much in doubt as to whether there is, in point of fact, an established sex factor in determining the red cell count—an item of obvious preliminary importance, deserving further investigation.

Whatever the fact as to sex differences, however, it appears

to be fairly established that the lymphocyte population of the child's blood, and in particular the large monocyte population, decreases with advancing age. This would seem to suggest (holding still to the Proteomorphic interpretation) that the adult organism is in general called upon to deal less comprehensively with the full-sized foreign protein molecule than is the organism of the child. A plausible explanation of this, as already suggested, may be found in the obvious needs of the growing organism, where nitrogenous tissue is being built up day by day; as contrasted with the adult organism, where the nitrogenous tissues are only holding their own, or are actually degenerating.

Incidentally, it may be supposed that the normally large equipment of mononuclear cells in the blood of the child and adolescent may account in some measure for the relative immunity to the growth of malignant neoplasms in early life. Contrariwise, the susceptibility of old age to the growth of such neoplasms may be associated with the decreased numbers, and, presumably, decreased functional activities of the mononuclear leucocytes chiefly concerned in handling unbroken proteins in general and lawless neoplastic cells in particular.

Further Hints as to Differential Functions

Such a suggestion is obviously consonant with the interpretation of the rôle of the lymphocyte and the large mononuclears put forward in connection with the Proteomorphic theory, and constantly reiterated in the present volume. It must be freely admitted, however, that our knowledge of the subject is at best fragmentary, and that a great deal more work must be done before we can hope for definite answers to many questions that obtrude themselves whenever one considers a blood smear with philosophical—that is to say, with childlike—inquisitiveness.

As provisional deductions from my own personal studies, I have suggested the possibility that one chief rôle of the polynuclear leucocytes may have to do with the metabolism of fats. Observation has taught me to expect to find a relative and absolute leucopœnia in examining the blood of obese patients of the anæmic type. It has just been remarked that bacteria are surrounded by a lipoid covering and have a body structure that incorporates lipoids. It is familiarly known also that the polynuclear has to do with the fight against bacteria—that being a classical observation of Metchnikoff that has hitherto stood almost alone as an interpretation of specific functions of a particular type of leucocyte. It is not improbable that lipoids also enter into the constitution of the cell membrane of the cells of the normal organism, and of such modifications of these cells

as go to make up the tissues of malignant neoplasms. If such is the case, and if the enzymes of the polynuclears have an important share in the digestion of fats, it may plausibly be assumed that the polynuclears have an important share in attacking the cancer cells, thus co-operating with the mononuclears. Reference was made to this possibility in the *Monograph,* in connection with the observation that partially degenerated polynuclears are observed to congregate, along with the mononuclears, in the region of a neoplasm that is undergoing disintegration.

It has been observed that large mononuclear leucocytes on occasion ingest bacteria and yet are unable to digest them. This may be because the monocyte does not produce an enzyme that attacks the fatty substances, and hence is unable to penetrate the cell wall of the bacterium. This initial stage of combating the bacterium being reserved for the polynuclear, and this function having been accomplished, the protein content of the bacterium, whatever its molecular status, may be turned over to the monocytes for further proteolysis, the ultimate product being handed on to the red corpuscle, according to the hypothesis of the Proteomorphic theory.

It is a familiar observation that a preponderant number of the leucocytes that spring into being when there is a marked bacterial infection are polynuclear in character. This is consistent with the above supposition that the activities of this particular type of leucocytes are necessary to begin the destruction of the bacterium. It has been further observed, however, that at a later stage of infection there may be a relative and absolute lymphocytosis. This is at least consistent with the supposition that the mononuclear leucocytes handle the bacterial proteins after the polynuclears have made their protein contents available by dissolving the lipoid membrane.

By way of recapitulation, and condensed summary, it may be recalled that under normal conditions, according to the provisional hypothesis on which I am working, the polynuclears are concerned with the handling of the fats normally in the blood, which somewhat exceed in amount, it may be observed, the foreign proteins normally present there. The handling of this normal fat, plus the handling of the bacteria that make perpetual onslaught, may account for the organic necessity of having the neutrophile population of the blood about three times as great as the mononuclear population. The relative paucity of the mononuclears, and in particular of the large monocytes, may perhaps be provisionally accounted for as explained by the paucity of unbroken foreign proteins in normal blood. In childhood, when these proteins are abundant, owing to the needs of the growing organisms, the mononuclears are relatively more abun-

dant; and we have seen that such is the condition also in untreated cases of cancer, and in various other conditions of disturbed protein metabolism, including intestinal toxæmia; subject, however, to the modifying consideration that an excessive stimulus may for a prolonged period have led to exhaustion of the blood-forming organs, bringing about a leukopœnia.

As opposed to this line of reasoning, it is perhaps worth considering that the polynuclear appears to be the most highly differential of leucocytes, and that inferentially it might be supposed to deal with the higher proteins rather than with fats and hydrolysis product. Obviously, the question calls for further experimental evidence.

As to the different types of large monocytes, I am disposed to regard lymphoidocytes, myelocytes of the different types, and cells of the kind designated by Papenheim as leucoblasts, as belonging to the same series with typical large monocytes, the latter being mature and actively functional examples of this type of cell. It is true that the myelocyte is usually regarded as of the granular series, and the large monocyte as of the non-granular; but, in my opinion, this distinction does not connote an actual difference of origin or ultimate structure, but only divers stages of development.

There is another type of large mononuclear leucocytes which I believe to be merely an overgrown lymphocyte. The presence of these large lymphocytes indicates activity of development of the lymphocyte population. Not infrequently in the course of Proteal treatment it will be observed that all the lymphocytes increase in average size, and many come to such proportions as to be classified as large lymphocytes, whereas at the beginning there was but a minimum number, or even none at all, of this type of actively functional lymphocytes.

Whereas the typical large monocyte (including the so-called "transitional" type), with its relatively deep-staining nucleus and basic cytoplasm, is the cell that I like to see represented in increasing coteries under Proteal treatment, I am disposed to think that the typical large lymphocyte works hand in hand, so to speak, with its congener in dealing with the foreign proteins. Whether one type of cell of a preference deals with the unbroken protein molecule and another with the partially hydrolyzed molecule (peptone, proteose) is a question regarding which opinion must as yet be held in abeyance, although observations are in hand that at least prepare the way for the ultimate elucidation of this aspect of the problem.

The fact that under Proteal treatment there is coincident increase in numbers and betterment of quality of large monocytes and of red corpuscles, suggests a possible common origin for these

two types of cells in similar regions of the bone marrow. Such origin would be consistent with the hypothesis that the large monocytes begin and the red corpuscles complete the process of protein hydrolysis.

That under normal conditions the large monocytes are few and the red corpuscles many, may be provisionally explained on the supposition that a large amount of protein matter normally enters the blood stream at the polypeptid stage, whereas the amount of unbroken protein is normally very small; in addition to which it is to be recalled, of course, that the red corpuscles have the further function of carrying oxygen.

It is, of course, generally accepted that the polynuclears originate in the bone marrow; but the fact that these very commonly decrease in number while the large monocytes and the red corpuscles are increasing under Proteal treatment suggests an independent site of origin as a possibility; with the alternative possibility that the genesis of different types of leucocytes may be dependent on a different stimulus to the mother cell rather than upon differences in the mother cells themselves. In any event, the relative decrease of polynuclears (and their absolute decrease when they originally were in excess) under Proteal treatment coincidentally with the clinical improvement of, let us say, a cancer case in which the neoplasm is regressing, suggests that whatever share the polynuclear may have in the decompounding of the foreign protein cell may be accomplished by a normal complement or even a subnormal complement of these particular agents. The reader who is familiar with the tables published in the *Monograph* will recall that the polynuclear count not infrequently falls to 55 per cent. or even to 50 per cent. of the total, and occasionally drops to 45 per cent., and even, in exceptional instances, to 39 per cent.

In general, as has been noted, under Proteal treatment, the polynuclear count tends toward the normal or slightly subnormal status, the small monocyte population being subnormal, and the large monocyte showing spectacular increase. For example, a table published in the *Monograph*, showing the blood count in 19 cases of cancer after an average treatment of 186 days, gave these figures: polynuclears, 57.1 per cent.; large monocytes, 24.8 per cent.; small monocytes, 15.7 per cent.; eosinophiles and basophiles making up the remaining 2.39 per cent. Another table presenting 31 cases after an average of 152 days of protein treatment showed: polynuclears, 64.4 per cent.; large monocytes, 18.3 per cent.; small monocytes, 15.6 per cent. Still another table, showing 48 cases of various kinds, including hyperthyroidism, intestinal toxæmia, tuberculosis, and cancer under protein treatment for an average period of 152 days shows the following:

polynuclears, 63.4 per cent.; large monocytes, 16.9 per cent.; small monocytes, 16.8 per cent.

In each of these groups of cases, it will be observed, the striking anomaly is the preponderance of large monocytes. That fact, however, is one that scarcely needs emphasizing for the reader of the present work. That such an increase does occur, as the direct result of protein treatment, and that this increase is associated in a beneficial way with the handling of foreign protein products in the system, are inferences that constitute the substructure of this book and the guiding principles of the investigations on which it is based. They are deductions from a wide range of original studies, and they are conceived to constitute a significant contribution to physiology, pathology, and therapeutics. That they constitute valid observations and deductions, I entertain not the remotest doubt. Nevertheless, I would repeat, in leaving this aspect of the subject, that there is no necessary association between the validity of these observations and deductions and the value of protein medication as a therapeutic agency.

In my original studies, clinical observation and microscopical observation have gone hand in hand. Each has found support in the other. But I repeat that my pioneer work with the microscope has not as yet been checked by the observation of any considerable number of cases in the hands of other workers; whereas the clinical results have been duplicated by some hundreds of physicians administering Proteals from my laboratory in accordance with my methods. Under such circumstances, it must freely be admitted that the clinical findings might stand though the microscopical findings and the theoretical explanations failed of corroboration. As I have stated, no one should condemn the method merely because he does not agree with the theoretical interpretation here presented.

Having made that concession, however, let me not leave the subject without reiterating my expectation that clinical observation and microscopical observation will both find abundant warrant in the findings of any competent observer who makes scientific investigation of the new method; coupled with the statement that the interpretation of the observed facts in the light of the Proteomorphic theory constitutes a working hypothesis that must hold the field until challenged by some new discovery of which we have no present inkling. In a word, repeating the phrase with which this book is introduced, and modifying it to fit the present purpose, it must be admitted that the observations and theories of protein metabolism and Proteal therapy presented in the foregoing pages are important if valid, and I have the utmost confidence that they are valid.

If I have dwelt rather longer on this aspect of the subject than might have been expected in a chapter ostensibly dealing with practicalities, it is because I would reiterate and emphasize my belief that protein therapy can be carried out to best advantage only with the aid of the microscope, and with a clear understanding of the underlying principles involved. The Proteals may indeed be administered empirically, by rule of thumb, and with only clinical results as a guide; but they may be administered to far better advantage if the clinical findings are checked day by day or week by week with microscopic observations of the blood.

Relative Non-toxicity of the Proteals

Let us turn now to matters that to the average reader may seem of greater interest or at least of more directly practical character. First and foremost, there is the matter of safety of administration—implied doubtless in the foregoing pages, but not hitherto dealt with explicitly and in detail.

The experiments in the administration of proteins to dogs and guinea pigs are of interest in this connection. It has been reported by independent workers that very small doses of bacterial toxins, including Coley's fluid, bring about a condition of toxicity, with notable cachexia, in the dog, that make it impossible to continue the administration for a considerable length of time without disastrous consequences. But, on the other hand, it is possible to administer the vegetable protein edestin in large doses without producing unpleasant symptoms of any kind, beyond a temporary slight chill and rise in temperature.

I have administered various vegetable proteins (extracted from more than a score of plant species in the aggregate) to guinea pigs week after week, while the animals maintained perfect health and normal growth; the dosage employed relative to the weight of the animals being from fifty to one hundred times the maximum Proteal dose employed therapeutically.

These laboratory observations are obviously in accord with my experience and that of many scores of associated physicians who have administered proteals to patients for long periods of time; and who have observed, in the vast majority of instances, a marked improvement in general health, and the disappearance rather than the onset of cachexia. Let us, however, examine this vital aspect of the subject somewhat more at length.

In the original presentation of the Proteomorphic theory, as reproduced in the present book, the idea was elaborated that all foreign proteins are primarily toxic, and that their relative toxicity, in their effect on any particular organism, is determined

largely by the duration of time and the frequency with which that organism has been subjected to their presence.

This principle was held to apply to the proteins that serve for food, and it was suggested that the reason why vegetable proteins in the foodstuffs are in general less toxic than animal proteins is that our primitive ancestors doubtless were vegetarians for many thousands of generations before they became flesh eaters. Making a somewhat more elaborate analysis, it is possible to make the application to many familiar foodstuffs. We are thus provided, for example, with an explanation of the familiar clinical fact that patients suffering from intestinal toxæmia, with its attendant sequels, may advantageously be placed on a vegetable diet, and that if animal proteins are allowed milk and cheese are more wholesome than red meat. It is a familiar practice with clinicians to permit invalids and convalescents to partake of these animal proteins, followed in due course by eggs, fish, and fowl, before permitting the use of beef or mutton; and it would appear that this clinical formula finds a certain measure of support in an analysis of the probable food habits of our prehistoric ancestors in successive evolutionary eras.

This point of view is recalled in the present connection to emphasize the fact that I have not overlooked the question of the toxicity of proteins in the inauguration and elaboration of the principle of non-specific protein therapy. From the outset, I have recognized that foreign proteins of every type are toxic and must be handled with discretion. But I have found them also to be agents having unique therapeutic possibilities when administered in proper dosage. And it is hardly necessary to point out that an element of toxicity is no barrier to the use of pharmaceutical agents; else we must forego the use of most of the best-accredited drugs in our equipment, from opium, belladonna, and digitalis to diphtheria antitoxin, typhoid vaccine, and salvarsan.

Nevertheless, the question of relative toxicity of different proteins is a highly important one. My experience shows that there is marked difference in the reaction obtained from the use of vegetable proteins, none of which could be considered toxic except in the general sense above outlined. Mustard seed proteins and rape seed proteins, for example, produce a much less severe reaction (when using the unbroken molecule) than the proteins of alfalfa seed and millet seed. It does not follow, however, that the former are the more valuable agents in therapeutics. Cases may arise in which it is desirable to produce the more powerful stimulus of the proteins to which the system has been less familiarized by past usage. In point of fact, in the case in question, the alfalfa and millet seed proteins have, according to my

observations, far greater therapeutic value than the milder proteins mentioned.

It should be explained that, whereas the introduction of vegetable proteins therapeutically into the parenteral system has been practiced extensively for a period of only about three and a half years, many cases have been under observation in which treatment with an animal protein (sheep serum) dates from a period much more remote—from five to ten years. The aggregate experience with the therapeutic use of foreign proteins introduced parenterally includes upward of four thousand cases directly observed or more or less definitely reported; and as the treatment of individual cases has usually been extended over terms of weeks or months, a single patient sometimes receiving upward of 300 doses, it will be seen that practical experience is sufficiently extensive to justify deductions meriting confidence.

The general conclusion which I wish to state in unequivocal and emphatic terms is that patients subjected for prolonged periods to the hypodermic administration of foreign proteins, including sheep serum and a variety of vegetable proteins, show no evidence, either clinical or hematological, of toxicity in the ordinary sense of the word, but, on the contrary, are robust of physique and normal of blood. Meantime the pathological symptoms for which the proteins were administered may have disappeared altogether or have been markedly modified for the better.

This, after all, is what might have been predicated from a knowledge of the fact that a certain amount of unbroken proprotein from the food finds its way regularly into the parenteral system from the digestive tract. In other words, every individual, in health and in disease, is more or less subject to continuous cytogenic stimulus from the presence of the food proteins in his parenteral system. To be sure, it has been suggested (by Metchnikoff originally) that this fact has to do with the ultimate development of symptoms of senescence with the passing of the years; and it is my personal belief that the presence of foreign proteins in excess, taken as food products with the ordinary diet, is responsible for a large measure of the maladjustments that are incident to and coincident with the development of what we term old age. Be that as it may, however, the case records cited in this book (together with those epitomized in tables of the *Monograph*) would appear to give final answer to the question whether a prolonged use of proteantigens in therapeutic dosage constitutes a measure necessarily detrimental to the patient. The records seem to show that, quite on the contrary, such administration may be in the highest de-

gree beneficial, and that the judicious use of proteantigens may stimulate the blood-forming mechanism to the effective combating of toxins both of bacterial and non-bacterial origin against which no other measure of corresponding efficacy is available.

I have already presented tables showing that the modifications of the blood count under proteantigen treatment may be, and frequently are, progressive in what I consider the right direction. I am preparing for publication in the new edition of the *Monograph* more elaborate series of tables in which blood counts of various patients are arranged sequentially as to time; beginning with a series of counts of untreated cases, and going on day by day to cases that have been under treatment for a term of months. For convenience of observation, these cases are arranged in successive groups by ten-day periods. This, it will be understood, is a purely arbitrary division, made merely to give opportunity to classify results and show at a glance the general effect of treatment given a variety of cases for shorter and longer periods of time. It will be seen that, generally speaking, there is a progressive or cumulative effect observable; that, in other words, cases that have been the longest under treatment are, on the average, those that show the most pronounced modification of the blood count in the direction of (a) higher hæmoglobin index, (b) increase of red corpuscles, (c) modification toward the normal of the leucocyte count, with (d) relative increase of mononuclear leucocytes, and in particular marked increase of large mononuclears.

If these facts are interpreted in the light of the Proteomorphic theory, it appears that the conglomerate group of patients here under consideration have benefited progressively by the proteantigen treatment, and that those that have been treated more or less regularly for periods of six months, a year, and even two years, are in better condition, as regards their blood count, than those treated for a shorter period. When it is further stated that these patients, observed as to their clinical condition, show a similar status of improvement, the case for the non-toxicity of proteantigens of types herein referred to (chiefly egg albumen, milk albumen, sheep serum, and the Proteals) may be considered to be fairly established.

I may add, by way of auxiliary evidence, that of the hundreds of physicians who have used the Proteals from my laboratory no one has ever reported a reaction giving occasion for the slightest alarm, much less a lethal effect; whereas testimony to the beneficial effects resulting, seemingly in direct consequence of the administration of the Proteals, has been so nearly unanimous as to satisfy the most optimistic anticipations.

The Preparation of the Proteals

It is perhaps unnecessary here to go into details concerning the various methods of extracting vegetable proteins that have been employed at one time and another in my laboratory. The chief facts of importance attach to the method that has superseded others, and has been employed in preparing the Proteals supplied to the profession during the past year, the results of the use of which are summarized in succeeding pages.

The method consists in the extraction of the proteins by boiling the ground seeds or other plant products in a very dilute solution of hydrochloric acid. Best results have been attained with most seeds by using 50 grams of the powder to the liter of water, and adding from 40 to 80 cubic centimeters of ten per cent. hydrochloric acid. With plant products other than seeds, such as alfalfa meal, 20 cubic centimeters of the dilute acid suffice. The mixture is boiled in a glass flask for four hours.

The decoction contains, of course, a mass of vegetable detritus that must be removed by filtering. There is marked variation in different products in their facility of filtering. With some it is necessary to refilter two or three times. The final filtrate is neutralized with 10 per cent. solution of sodium hydroxide. Just beyond the neutralization point a precipitate forms, part of which is redissolved. The solution, meantime, becomes of a darker color, varying from amber to a deep claret according to the constituents.

Either before or after filtering, as a matter of convenience, the solution is evaporated at low temperature under a hot air draft until it bulks about 300 cubic centimeters (varying from 200 to 400 with different products). The solution has usually become slightly acid again, and it is necessary once more to neutralize with sodium hydroxide. It is important that slight alkalinity should be attained and preserved; otherwise, the extract will be painful on hypodermic administration.

The Kjeldahl nitrogen test is now made, after which the solution is either further evaporated or diluted with normal salt solution, as the case may require, to bring it to the standard strength of three milligrams of nitrogen to the cubic centimeter; indicating a protein content of slightly less than two per cent.

The extract thus standardized is placed in ampules and sealed in a Bunsen flame; then sterilized discontinuously for three days in an ordinary sterilizer.

There are, as a matter of course, tricks of manipulation facilitating the preparation of the Proteals that vary somewhat with the different products; but, as will be seen, the process is, on

the whole, a very simple one. It may readily be duplicated in any laboratory having a moderate equipment for physiological chemistry.

The proteins thus prepared contain alkali albumens, proteoses, and a variable quantity of peptones. It is obvious that the relative percentages of the products of partial hydrolysis will vary with the degree of concentration of acids in the original medium and the length of time of boiling. The whole-plant products, like alfalfa meal, being boiled in weaker acid solution, are less extensively hydrolyzed, and their proteins have been observed to be much more likely to produce a local anaphylactic response. Whether there are compensatory advantages in this is a question that I am not as yet prepared to answer definitely; but I have observed a good many cases in which the local reaction appeared to be followed by a beneficial systemic response.

In this connection it may be observed that the earlier extracts, prepared without boiling, in simple salt solution or in solutions of sodium hydroxide, and containing the full-sized protein molecule, produced a much more severe local reaction, and occasionally a general anaphylactic reaction; and that it was at first supposed that the production of a pronounced reaction was therapeutically desirable. The independent workers who in June, 1916, and subsequently reported the use of proteoses and of bacterial vaccines as non-specific agents, as in the treatment of typhoid fever and arthritis, have employed a dosage (one or two c.c. of a four per cent. albumen solution) that produced very marked systemic effects, as well as a pronounced leucocytosis; and some of them at least have associated the observed clinical benefits with the febrile reaction.

I have no doubt that there are cases where heroic dosage is desirable, but in general the application of Proteal therapy, as I use it, calls for small doses, not producing marked systemic reactions.

The Proteal that has been used most extensively during the past year and a half, and sent out from my laboratory in largest quantities to members of the profession, is No. 45, the combination of equal parts of the proteins of alfalfa seed, alfalfa meal, and millet seed. The same combination with the addition of the proteins of rape seed and mustard seed bears the laboratory number 65. A newer combination, much less extensively tested as yet, contains the proteins of red clover seed, cotton seed, flax seed, hemp seed, and carrot seed, and bears the number 75. A still more comprehensive combination, containing equal parts of the proteins of the ten different types just listed (a mixture, in other words, of No. 65 and No. 75), is known as Proteal No. 100.

The question naturally arises as to whether there are thera-

peutic advantages in using a combination of proteins rather than a single protein. I believe that experience does not as yet justify a positive answer. I have studied the matter very carefully through observation both of clinical symptoms and the blood response, and I am not prepared to say positively that I have seen decisive evidence of a difference, qualitative or quantitative, between, for example, the use of Proteal No. 39, which contains only the protein of alfalfa seed, and Proteal No. 45, which contains also the proteins of alfalfa meal and millet seed. It is difficult to avoid the feeling that there must be a difference, but this may be based merely on a preconception. I have thought it worth while to test the validity of the preconception by making the elaborate combinations above listed, and numerous others. I think the matter will not be definitely settled until many thousands of cases have been treated with single proteins and with proteins in combination. There would seem to be theoretical warrant for the assumption that, inasmuch as each protein has its own individual response, a combination of proteins would produce a more varied and, in the aggregate, a more pronounced response than a single protein. But whether or not this should prove to be the fact, there is nevertheless abundant reason for making the combinations, inasmuch as they give opportunity for the introduction of a new type of protein from time to time, in accordance with the established therapeutic principle that it is desirable to change the type of protein, or introduce a new type, when a certain degree of immunization or cytogenic apathy has been produced.

A convenient practical method, for example, is to begin treatment of a case, let us say, of tuberculosis, with Proteal No. 39, alfalfa seed protein; shifting presently to a combination of alfalfa seed and alfalfa meal (Proteal No. 60), and then in due course to No. 45, which introduces millet seed protein as an additional element. A little later the shift may be made to Proteal No. 65, which, still retaining the alfalfa and millet proteins, introduces also the proteins of rape seed and mustard seed. Still later an entire shift may be made to No. 75, with its five new proteins, or to No. 100, which retains the original proteins in relatively reduced quantities and introduces five new ones.

An alternative procedure, which has been observed to work well in many cases, is to begin with a combination, say No. 45 or No. 65, and after a time to shift to a single one of the constituents. For example, begin with the combination containing alfalfa seed, alfalfa meal, millet seed, rape seed, and mustard seed (No. 65), and presently shift to No. 39, alfalfa seed protein alone, beginning with a relatively small dose and increasing gradually, until, obviously, at maximum dosage the maximum re-

sponse from that particular protein may be expected. After that one may shift to millet seed protein (No. 38) or rape seed protein (No. 42), and so on. The advantages of such a transition are that it enables one to begin with a mild general response and presently to get the maximum effect from an individual protein.

The response to the combined proteins would be, theoretically, varied and comprehensive; the response to the single protein restricted, but relatively intense.

The experienced physician will use his own ingenuity in making application of these principles, just as he does in combining drugs in his ordinary prescriptions. Every skilful practitioner uses combinations of drugs having allied effects, in the confident belief that he is attaining certain results at least a little better than could be secured from any one of the individual constituents. Yet he might find it difficult to prove this. Similarly, some users of the Proteals come to feel that they get results from combinations that they do not get from the individual proteins. I repeat that it remains for the future, with its analysis of thousands of cases, to justify or refute this belief.

Meantime it is not in the least in doubt that each type of protein produces its own individual response, and that one protein may not be substituted for another indifferently. That a system immunized to large doses of proteins of one kind or combination, for example, will show the most vigorous reaction when a new protein is introduced, has been demonstrated over and over in my experience, particularly in the early days when working with the unbroken proteins.

This is tantamount to saying that, whereas the Proteals are thus standardized on the basis of the same amount of protein in each, it does not follow that each one is the equivalent of the other in its therapeutic action. It is my opinion, as the reader of the foregoing pages is aware, that the protein response is always similar in character and to be interpreted in the same physiological terms. But it has already been pointed out again and again that some Proteals produce much more active response than others. The explanation offered has been that proteins to which the system has longest been accustomed and most continuously experienced will produce the least striking reaction.

Specific Properties of Non-specific Proteins

To speak of the specific properties of non-specific proteins would appear to be, on its face, a contradiction of terms. But the phrase has definite meanings that are clearly intelligible. The word "specific" as employed in connection with the use of pro-

tein remedies refers, as is well known, to the use of the bodies or toxins of definite character of pathogenic bacteria to combat conditions associated with the activities of the same type of bacteria. The use of anti-typhoid vaccine either as a preventive against typhoid fever or as a curative agent when typhoid fever has actually developed, is the classical illustration of the specific use of a specific protein remedy.

But the same vaccine may be used, and in point of fact has been used with apparent effectiveness in the treatment of rheumatoid conditions; and in such a case the vaccine is used non-specifically. In the latter case the response evoked or desired has no association with the typhoid bacillus, but is a general protein response. Doubtless there is a specific response also, but this is purely incidental and does not enter into the calculations of the therapeutist.

When vegetable proteins extracted from the seeds or substances of higher plants are used there is obviously no chance for a specific response in the sense in which the word has just been defined. Observation shows that there are certain very characteristic modifications of the blood that occur in response to the parenteral introduction of any of these foreign proteins, and that similar modifications are brought about by the introduction of various animal proteins, for example, sheep serum. In the practical use of the Proteals it has been found possible to substitute one for another, the selection of the particular type of protein to be used in beginning treatment of a given case being to a considerable extent a matter of indifference. I early observed, however, that some types of vegetable proteins produced a very much more pronounced anaphylactic response than others, and I soon found myself selecting one protein or another with definite reference to the observed condition or suspected idiosyncrasies of the particular patient.

This obviously implies a recognition of specific differences among the vegetable proteins used non-specifically.

Further proof of such differences were found in the fact that an individual patient sometimes responded much more actively to one type of protein than another. An injection of alfalfa proteins, for example, might cause a marked local reaction, whereas when mustard seed or rape seed protein was substituted no reaction occurred. Further proof of the specific action—in the usual sense of the word—was given when it was found that the patient who had become in a measure immunized to the effect of one protein showed new response on exhibition of another protein.

Reasoning from analogy, we may suppose that the relative non-toxicity of proteins from food plants will be shared in some measure by proteins from botanically related species of plants.

Thus food plants and their allies would furnish proteins to which the system was relatively immune; whereas the plants lying botanically rather far afield from the food plants would furnish proteins of relative activity or toxicity. Experience, so far as it has gone, tends to confirm this supposition. In selecting plants for the development of new Proteals, I am guided by this principle. Among the newer extracts, for example, the clover proteins may fairly be expected to produce more pronounced response than the proteins of oats and wheat.

It may be added that the theory finds further confirmation in the fact that the proteins of white of egg and of milk, which I have used somewhat extensively in alternation with the various Proteals, give a still milder reaction, so I was accustomed, while experimenting with them, to standardize them in a three per cent. solution and give them in the same dosage that was employed with the two per cent. Proteals.

All this clearly implies specific differences in the therapeutic action of the non-specific proteins. If the conclusions just given are justified, it is obvious that here is a field for investigation of very wide possibilities. The plants from which I have hitherto extracted proteins for therapeutic use number fewer than thirty species; it would be difficult to put a limit upon the number that might advantageously be tested.

The Administration of the Proteals

It is my custom to begin the treatment of every new case with doses of only three or four minims of any one of the proteals; and administering treatment usually on alternate days, but sometimes daily, to increase minim by minim, or, if there is no reaction, two or three minims at a time till a maximum dose is attained.

The size of the maximum dose varies with the individual case. Where there is profound protein toxæmia, as in a well-developed cancer subject, it is usually desirable to run the dose up rather rapidly to 10, 15, or even 20 minims; sometimes a good deal beyond this. Doses of 60 and even 90 minims of the original proteal extract have been given. I formerly thought it desirable to push the dosage until a fairly severe general reaction (rise of temperature, quick pulse, chill) was produced on at least one occasion. Prolonged experience, however, in which clinical symptoms were observed in connection with the blood-count modifications, leads me to question whether this is usually desirable, even in cases of malignancy; and it is not in the least degree necessary to secure a general reaction in dealing with the milder

types of toxæmias associated with secondary anæmias and neurasthenia.

In cases of the latter type a maximum dose of 5 to 8 minims usually suffices, and often results of the most conspicuous and well-defined character may be attained with a dosage of only 4 or 5 minims.

In general, my present tendency is to use small doses, and if necessary give them more frequently, rather than to force the dosage to heroic proportions. With the new proteals there is no objection to frequent administration, as the giving of the hypodermic is practically painless.

Probably the most satisfactory method of treatment, whether of simple toxæmias or malignant ones, is to administer a given Proteal in gradually increasing doses until the maximum dose considered desirable in a given case is reached—that is to say, a dose that produces a satisfactory clinical progress and characteristic modifications of the blood count; to hold to this maximum dose for a week or ten days; and then to shift to another proteal, beginning with a dose of three or four minims and working up the scale as before. It should be remembered that each protein elicits its own response, and that a patient relatively immunized to, let us say, mustard seed or rape seed proteins may react vigorously to the protein of alfalfa. The rule is, in beginning with a new protein, to start with a minimum dose, no matter how thoroughly accustomed the patient is to the administration of other proteins.

Similarly if the patient has discontinued the Proteal treatment for a considerable period, and then begins it again, even with the same Proteal, it is well to start in with a small dose, but in this case the dosage may be increased much more rapidly than with a new patient.

It is my routine practice to administer the Proteals by fairly deep subcutaneous hypodermic injection into the back of the upper arm. Intravenous injection has sometimes been employed, but this produces a severe anaphylactic reaction the desirability of which is doubtful unless in very obstinate and intractable cases. I do not advocate or practice the method of heroic dosage, with emphatic anaphylactic reaction, that a few physicians who in recent months have advocated non-specific protein therapy with the use of vaccines appear to have employed. My own experience, based on study of a far larger number of cases than have elsewhere been treated with non-specific proteins in the entire world, leads me to conclude that the milder method of administration is equally efficacious in the end, while being devoid of unpleasant features.

It is obvious that patients suffering from a simple anæmia

or a mild intestinal toxæmia would not submit to a treatment that involved the production of a severe anaphylactic reaction. In such a case the remedy would be considered worse than the disease. Fortunately nothing of the kind is either necessary or desirable. Such a patient undergoing Proteal treatment submits to nothing more disagreeable than a painless hypodermic, followed at worst by a very slight tenderness at the point of injection, and with no general reaction whatever except the pleasurable one of increased bouyancy and enhanced sense of well being.

Such, then, are the essentials of the technique of Proteal therapy at present developed. I greatly mistake if the method does not constitute a marked advance upon any therapeutic measure hitherto available for treatment of the varied groups of conditions of disturbed protein metabolism—ranging from simple anæmias to tuberculosis and cancer—to which it is applicable.

Let us now turn from generalities to particulars and consider very briefly the salient aspects of the application of the Proteal method to the different types of protein toxæmia in question.

Proteal Treatment of Cancer

The reader is aware that the fundamental fact upon which Proteal therapy is based is that the parenteral administration of a foreign protein in suitable doses leads to a systemic response characterized by rejuvenation of the blood corpuscles. The indirect result of such rejuvenation is, in effect, the enhancement of the phagocytic and enzymic forces with which the body combats protein invasion of all kind. This includes, obviously, cells of the type called malignant.

Incidentally, therefore, Proteal therapy is applicable in the treatment of cancer. As I have written another book on this aspect of the subject, I shall here summarize my experience in this field very briefly. In so doing, perhaps, I may be permitted to incorporate matter from a popular article in which I gave a condensed account of my experience. Possibly the present reader, sated with technicalities of recent pages, will find this popular summary a refreshing change. The reader who wishes fuller and more technical information as to the status of the Proteal treatment of cancer may turn to the Monograph just referred to, which under the original title of *The Proteal Treatment of Cancer and Allied Conditions,* is about to be issued in a second edition.

The condensed popular presentation which, taken in connection with repeated references in other chapters, seems fairly adequate for the present purpose, is the following:

Wherever the cancerous condition develops there is always pro-

found disturbance of the blood, evidenced among other things by modifications in the quality of the red corpuscles and the relative numbers of the different types of white corpuscles. Cancer is never a merely local condition.

To put the matter in untechnical language, the corpuscles fight the developing cancer cells; if they win, the cancer is eliminated. The development of a cancer of tangible size is proof positive that the corpuscles have lost the fight. It may plausibly be argued that if a way could be found to increase the cohorts of corpuscles, and to increase their fighting capacity, the tide of battle might be turned, and the corpuscles, hitherto defeated, might now become victorious against the cancer cells.

When the Proteals are administered hypodermically, rejuvenation of the cohorts of blood corpuscles takes place. That is a simple matter of fact, which I have demonstrated hundreds of times under the microscope. My observations have been confirmed by numerous independent workers. It has further been observed that the physical condition of the cancer patient very generally undergoes a marked change soon after the Proteal treatment is instituted. Even where cancer had reached a late stage, perhaps following successive operations, and was now inoperable and supposedly hopeless, marked changes of favorable character have been observed repeatedly.

I have personally collected and published reports of 766 such cases, treated by more than one hundred and fifty physicians, showing that, in the estimate of the physicians themselves, 64 per cent. of these "hopeless" cases showed conspicuous improvement under the non-specific protein treatment.

In a certain number of these cases the improvement continued until the physician regarded the patient as clinically well. The percentage of such seeming recoveries was small; but that a single supposedly "hopeless" case could be thus reported in the early stages of the use of a new method of treatment was in the highest degree enheartening. To the observers of such a transformation the result seems to border on the miraculous.

Even where the ultimate results fell short of this there were temporary effects in a large proportion of cases that seemed decidedly worth while. For example, in response to a special request, I received reports at one time from 142 physicians covering 284 inoperable cases. The reports came from 37 States and from several provinces of Canada, all the physicians being men of recognized standing. The specific preliminary results in this group of cases were as follows:

Where pain was present, it was favorably modified by the non-specific protein treatment in 77.4 per cent. of all cases. Generally the use of stupefying opiates could be discontinued. Where

an offensive discharge was present, it was favorably modified in 85.6 per cent. of cases. The general health of the patient was modified as to appetite, sleep, color, weight, or strength in 70 per cent. of cases. Mental attitude was favorably modified in 71 per cent. of cases. The condition of the cancer mass itself was favorably modified in 69 per cent. of cases, with marked regression in size in 27 per cent.

In reporting these results to a professional audience, I added this comment: "Dealing, as the statistics do, with supposedly hopeless cases, in the presence of which the physician has hitherto stood powerless, and with symptoms mostly not susceptible of amelioration by any agency hitherto available, this is a showing at once amazing and enheartening."

A few months later I was able to establish the important new principle that it is not possible to get cumulative and optimum results from the use of a single protein or combination of proteins, inasmuch as the system develops a degree of immunization. It was found that a case that had become static, after a period of progress, might take on a new response when a new type of protein was administered. This principle has been borne constantly in mind in my personal use of the Proteal treatment, and I have inculcated it persistently in advising with associated physicians. Perhaps it will be of interest to reproduce here a brief history of the patient upon whom the experience of shifting from one type of protein to another was first made:

Case of Mrs. V. Cancer of the left breast removed by surgeon in September, 1915. Recurrence above the clavicle and about the neck; pronounced inoperable. Non-specific protein treatment (hypodermically into the upper arm) begun in September, 1915. Striking modification of the blood, steady improvement of general condition, and fairly rapid regression of the cancerous mass. In June, 1916, only a few small enlargements remained, but these appeared to be static. A new Proteal, extracted from alfalfa seed, was administered, and the masses at once regressed, until only a single gland, as large as the little finger-nail, was observable just above the clavicle. This was excised with local anæsthesia, the incision healing promptly. Occasional doses of Proteal were given at lengthening intervals, and the patient is still under observation; but she has been to all appearance perfectly well for the past eighteen months. She is of normal weight and appearance; does housework energetically; reports herself as feeling as well and as strong as ever in her life. This, it will be observed, two years after the case had been pronounced hopeless by the surgeons, the diagnosis of cancer of malignant type having been confirmed with the microscope.

The value of a shift from one Proteal to another, illustrated by the above case, has been demonstrated over and over. Many types of vegetable proteins are now extracted in my laboratory, and new ones are constantly being tested. It is routine practice to shift from one Proteal to another in the treatment of any intractable case. To a large extent the different vegetable proteins are interchangeable, but no single one can produce optimum results unaided.

As illustrating the possibilities of the Proteal method in its present state of development, I may cite the history of a case even more striking than the one just presented:

Case of Mr. F. Carcinoma of the stomach. Operated on in September, 1916, by surgeons in Cincinnati, who found a cancerous mass completely filling the pyloric end of the stomach and involving the liver. No attempt made to remove the mass, but an opening was made in the front side of the stomach and the intestine attached to permit passage of food. The case was regarded as absolutely hopeless. The patient came to me for Proteal treatment five months later, February 25, 1917, in desperate condition, regarded by his friends and physicians as beyond the reach of medication. The response to Proteal treatment (administered hypodermically into the back of the upper arm) was immediate. Rapid transformation took place in the blood conditions, appetite improved, and the capacity to assimilate food. Strength was gained from day to day. Painful swellings of the knee joints, which had been a distressing complication, disappeared. The cancer mass in the abdomen, which could be readily felt through the emaciated abdominal wall, decreased rapidly in size until it was not more than one-fourth its original dimensions. For a time the patient did not gain weight; then he began gradually and steadily to gain, and in nine months he had put on twenty pounds. When the treatment was begun in February, the patient did not attempt to leave the house unattended. Eight months later he made a trip by himself from New York to his old home in Cincinnati to attend a banquet, participating actively in all the festivities associated with the event, and reporting himself, after returning to New York, as feeling in tip-top condition. He was received by his old friends and associates almost as one risen from the dead. Whatever the future progress of his case, there can be little question that the life of this patient has been extended by many months solely by Proteal treatment.

To show that similar results may be attained by physicians who have had comparatively slight experience with the Proteals, I may cite a very brief report from a physician in the North-

west, that chances to come to me just as I am writing this article:

"Mrs. A. O. Age 53. Cancer of the stomach. Small tumor at pyloric size of walnut. Under Proteal treatment tumor disappeared. Stomach symptoms (nausea, vomiting, pain) disappeared. No more blood discharges. Blood picture improved. Strength and general condition improving."

It will be observed that I have not used the word cure in connection with the Proteal treatment of cancer. The word cure is one that I shall not use until at least five years have elapsed after the clinical recovery of a cancer case. I am hopeful, however, that ultimately such reports may be possible. This hope finds justification in the fact that some of the cases that have been longest under treatment have shown no tendency to recurrence. Here, for example, is the record of a case treated by Dr. E. H. Williams, of Los Angeles, and reported by him in the *New York Medical Journal* of October 9, 1915.

Patient with recurrent inoperable cancer of the neck. Treatment begun in June, 1915. Patient made spectacular progress under hypodermic treatment, the cancer mass regressing rapidly and altogether disappearing in less than a month. The patient has now had no treatment whatever for more than two and a half years, and he continues in apparently perfect health. There has been no tendency to return of the cancer, and no manifestation of abnormality of any kind.

On the day on which the copy for this chapter goes to the printer, a letter comes to me from physician number 746 (my office files), of New Hampshire, telling of a cancer patient, a woman, treated by him so effectively with the Proteals (No. 45) that in October, 1917, she was "in fair health and strength, and able to do very good work in an eating saloon, acting as table girl," with "no evidence of cancer about her system," and now, having found the work of lifting the waiters too heavy, she is occupied regularly in a factory, and has gained fifteen pounds in weight, is of good color, and seemingly well.

With such reports as this coming from physicians in various parts of the world, many of whom are quite unknown to me personally, to fortify my individual observations, I feel amply justified in reiterating the statement that the results of the Proteal treatment of cancer are in the highest degree encouraging and enheartening. It would certainly seem within bounds to say that the Proteal method offers new hope for cancer sufferers everywhere in the world.

In some of my addresses to companies of fellow-physicians I have gone a step further, venturing the prediction that Proteal treatment will in the immediate future assauge far more

suffering than the world war causes, and will within the present generation save ten lives for every one that the war exacts.

Proteal Therapy and Rheumatoid Conditions

Through circumstances with which the reader of earlier parts of this volume is familiar, the original proteal extracts were at first administered solely to cases of inoperable cancer. But it was inevitable that any one who thoughtfully regarded the observed results of this treatment—noting in particular the blood modifications—should question presently whether maladies of kindred origin might not fall within the scope of the protein treatment.

At a very early day I suggested the possibility that a remedy producing such striking modifications of the blood should be applicable to the wide range of affections, bacterial and otherwise, associated with modifications of the blood count. It was agreed that tests as to this might advantageously be made as soon as experience was well grounded.

It chanced, however, that the observations tending to confirm the opinion that the proteal extract might have wider application were made by a New York physician quite by accident. Among the patients that came for treatment while the protein method was still in its infancy was a woman with cancer of the breast, who also suffered from a severe arthritis of many years' standing.

A published account of this case has described the condition of the patient before treatment as follows:

"The arthritis had affected the joints of the hands, wrists, elbows and ankles. The patient had had a variety of treatment without effect and suffered at the time when she was first seen more from the pain of the arthritis than from the recurrence of the malignant growth. The joints of the hands showed the most deformity, there was a typical ulnar deflection, the articular surfaces were enlarged and in some joints eroded, the hands could not be used for any useful purpose, there were frequent exacerbations accompanied by increased swelling and redness of the joints and increased pain. The affected joints served, in fact, as so many of them do, as a barometer of the weather conditions."

The case is not the less interesting because, as already noted, the treatment was aimed entirely at the relief of the returned cancer of the breast, with no thought, originally, that the rheumatic condition would be in any way affected. The treatment, aside from general hygienic precautions, consisted exclusively of the hypodermic administration of the original proteal extract. Note now the sequel:

"At the time the patient began the treatment she could not use her hands for any purpose and walked with difficulty. The injections were administered every second day in gradually increasing doses, beginning with ten minims. During the course of the first three weeks they were increased to twenty minims. At this time my attention was called by the patient to the fact that she now used her hands, for the past week had practically no pain, was able to button her clothing and was relieved of the discomforts of the disease to a degree which she had not experienced in years. This improvement continued so that from this time on the patient practically suffered no more pain from the diseased joints. The use of the hands gradually returned so that she was able to write, she could use a needle for sewing and, while the bony changes were in no way influenced, the surrounding inflammatory swelling did decrease and she continued in comparative comfort."

The observer was naturally impressed by these changes in the joint conditions, and he was quite unable to explain them except upon the basis of the effect produced by the protein medication. Very naturally, he recalled the circumstances of this case when a second patient who was suffering from a rather rapid development of arthritis of similar character came under his observation. This patient was a woman 36 years of age. The history of her disease extended over a period of two years, the joints involved being those of the hand, wrists, elbows, ankles, and knees. The patient had suffered intense pain.

The condition of this patient before treatment is described as follows:

"The bony changes were not as pronounced as in the case of the first patient, but the development had been more acute, the history extending over a period of approximately two years. She had already passed through the hands of several physicians who had employed various therapeutic measures, including careful dieting and observation of the gastro-intestinal tract, vaccination from cultures obtained from the teeth and a further course of vaccination with a mixed vaccine originated by Schaefer. The combined vaccines of Schaefer had given some relief, but had produced violent constitutional reactions which had been unfavorable to the general health of the patient. At the time of her first visit she was suffering so intensely that she could not walk and was carried into my office. I could not find a source of infection that seemed adequate to explain the difficulty."

This patient was at first treated by regulating of diet and attention to general hygiene, together with the administration of thyroid and thymus extracts. In the course of one month some mild

improvement had resulted from these measures. Then the striking changes observed in the first patient, as above noted, led to the decision to administer the Proteal treatment in this second arthritis case, although the treatment had theretofore been applied solely to patients suffering from cancer. The administration of the Proteal extract was begun on the 28th of May, 1915.

The injections were continued over a period of nine months. At the outset the patient had been taking 40 to 60 grains of aspirin each twenty-four hours to relieve the pain. The amount was promptly diminished in the course of the first three weeks of the Proteal treatment, and in the course of two months the drug was entirely discontinued.

Here is the report on the treatment and its results:

"During the earlier months of the treatment the injections were given every second day, during the last four months the interval between the injections was gradually increased until finally an injection was given only once a week. The patient's improvement was gradual but definite, and she finally reached and maintained a state of health satisfactory in every respect. The bony changes about the affected joints have never been relieved and it seems very doubtful if they ever will be. However, the infiltration and thickening of the soft tissues has been entirely relieved. During the past six months this patient has had no treatment whatever. She has been in excellent health, has gained twenty-four pounds in weight during the course of the treatment, and during the past summer has been unusually active, playing tennis, swimming and doing a variety of household work, using her hands with perfect freedom and comfort for such mechanical operations as writing, fine sewing, etc."

The clinical progress of this case was matched by the modifications in the blood conditions. Starting with a red blood count of a little over two million and hemaglobin of 70 per cent., the records show that on the 17th of September the red blood count was 3,900,000, the hemaglobin 79 per cent. On the 14th of December the red count was 4,444,000, the white count 6,700, the hemaglobin 90 to 95 per cent. On the 27th of December the red corpuscles numbered 5,280,000, the white corpuscles 8,000. The differential count, at a time when the treatment was most actively pursued, showed 53 per cent. polynuclears, 25.5 per cent. large monocytes, 12 per cent. small lymphocytes, and 9.5 per cent. eosinophiles. At a later date (December 27th), when the patient was receiving only weekly Proteal treatment, the differential count showed polynuclears, 14.5 per cent. large monocytes, 22.5 per cent. small lymphocytes, and 3 per cent. eosinophiles.

It is significant that two years have now elapsed since treat-

ment was discontinued in the case under consideration, and that the patient remains in a condition of normal health. She was under treatment for hay fever for a short time during the summer following the disappearance of her rheumatoid difficulties, but there has been no evidence of a tendency to recurrence of the old malady.

In recent months a number of cases of arthritis of various types have come under treatment in my office. Reports have come to me also from other physicians who have used the Proteals from my laboratory in the treatment in cases of rheumatism of various types. The evidence as a whole is not yet in any wise comparable to the evidence regarding the Proteal treatment of cancer, but in the main it is corroborative of the observations above recorded. Patients suffering from the most intractable forms of arthritis have had their pains banished and their rigid joints made mobile. Patients suffering from milder types of rheumatism have shown amelioration of the unpleasant symptoms and conspicuous improvement in the general condition—together with a characteristic regenerative modification of the blood—almost from the outset. With cases of the latter type doses of 5 to 10 minims of one of the standard Proteal extracts —for example, No. 45—have proved efficacious. For the more severe cases the dosage has been advanced, gradually, to 15, 20, and even 30 minims. But I have not thought it necessary or desirable to force the dosage to the point of producing severe reactions as a rule. I believe the best results are attainable by giving relatively small doses for a long period of time.

Spectacular results through the use of one or two heroic doses have been reported in recent months by physicians using the proteins of the typhoid bacillus; but it is my opinion that the method designed to bring about slow and gradual modifications in the affected joints will be found in the end more efficacious, as it is unquestionably the more pleasant method of treatment.

Details of technique aside, however, it would appear that the evidence justifies a large measure of confidence in the possibilities of treating rheumatsm and various rheumatoid conditions with non-specific proteins—associated, as a matter of course, with general hygienic measures, including low protein (and chiefly vegetable protein) diet and systematic exercises.

Dietetic Anomalies Explained

As to diet, however, I would offer a suggestion, which will perhaps seem anomalous; but which is based on a wide range of experience in the first instance, and supported theoretically by the fundamental principles of the Proteomorphic theory. It

is to the effect that, whereas I advocate a low protein diet for people at middle age and later, in health and in toxæmic maladies, and in particular a low animal protein diet, with emphasis on the exclusion of bearers of purin-bases for rheumatoid cases, I nevertheless believe it advantageous occasionally to permit the patient to depart from the rule and indulge in a meal including a moderate portion of meat—for example, about three cubic inches of beefsteak.

It is a familiar experience that such a meal, indulged by exception and not too frequently, has a stimulative or tonic effect. Haig explains this, as will be recalled by every one familiar with his oft-berated but never discredited work on Uric Acid, on the assumption that the beef tends to acidify the liver and cause that organ to sieve the uric acid out of the blood temporarily—an explanation that appears to me altogether fanciful and fallacious. Doubtless my own explanation will seem equally fanciful to any one who has not grasped, or does not accept, the fundamental thesis of the Proteomorphic theory. Be that as it may, my explanation is that a certain amount of the protein of the steak is pretty sure to find its way into the parenteral system not fully decompounded (experiments cited in earlier chapters fully warrant this assumption), and will thus act as a proteantigen stimulating corpuscular response precisely as if it had been introduced hypodermically. In effect, eating the steak was equivalent to giving treatment with a protein of a type which is not familiar (since the meat is eaten only at rather long intervals), and against which the system is not at the moment fully immunized.

The corpuscular response includes, according to hypothesis, increased enzymic activities of the corpuscles; enhancing, therefore, the purin-body-reducing functions of the erythrocytes, and thus tending to clear the blood of uric acid—in accordance with Haig's statement of the fact, but not at all in accordance with his explanation of the *modus operandi*. The increased activity of the red corpuscles and their consequent excessive destruction in the liver might indeed be said to "acidify" that organ, through increased influx of uric acid, and in particular urea, from the bodies of the disrupted erythrocytes; but the "sieving" process, according to the present thesis, would consist in the increased capacity of the erythrocytes to transform uric acid into urea (see Chapter I above).

Meantime, of course, the beef protein ingested, if entering the parenteral system more or less fully digested, but short of the amino-acid stage, would bring an increment of purin bodies that would add to the uric acid supply. Where the balance would be struck, in any individual case, would depend upon the

quantity of meat ingested and the length of time that had elapsed since the organism had been habitually invaded by this particular protein. It is consonant with the Proteomorphic conception to assume that even when the beef protein-products entered the blood at the polypeptid stage, they would act as antigens directly stimulating the mother-cells of the erythrocytes and the enzymic response of the erythrocytes themselves—provided always that these cells were not sated by habitual presence of these particular proteins.

Should intestinal digestion be so perfect that all the beef protein is reduced to the amino-acid stage before passing into the parenteral system, there would no such antigenic effect—nor, in all probability, would purin bodies be included; but there is reason to believe that enteric digestion seldom is so perfect as this—particularly in case of persons of rheumatoid diathesis, since they, almost by definition, suffer from intestinal toxæmia. Indeed, as was earlier pointed out, it is not quite certain that the proteins do not normally enter the blood as polypeptids.

Such, then, is the theoretical reasoning through which I find warrant for the practice of admonishing my patients—rheumatoid, anæmic, cancerous, tubercular—to regard an occasional, but not too frequent, infraction of the purin-free diet rule as a part of the rule. The radical distinction between such occasional indulgence and habitual ingestion of the purin-bearing proteins will be obvious to any one who recalls the oft-reiterated principle that an incessant stimulus from the constant invasion of a protein of any type leads to the corpuscular exhaustion implied in what has been repeatedly spoken of (though perhaps the phrase in this connection is not very defensible) as immunization to the effects of a given protein.

Incidentally it may be noted that the utter satiety that attends the too continuous ingestion of a single type of foodstuffs is thus to be explained. So far as I am aware, no other really intelligible explanation of this anomaly has hitherto been forthcoming. The oft-cited paradox (doubtless not literally true, yet symbolizing a profound dietetic truth) that no one can eat a quail a day for thirty days without utter satiety, thus finds scientific elucidation.

Proteals in the Hands of the Practitioner

All this, however, is carrying us afield from the question of the treatment of rheumatoid conditions with Proteals—though, after all, not far afield, as will appear when an explanation of the action of the Proteals in this connection is given a little later. First, however, it will be well, as establishing the prac-

tical status of the Proteals in the matter, to cite a few individual experiences of physicians using Proteals from my laboratory in the treatment of familiar types of chronic arthritis. Here, for example, is an informal letter from physician number 726 (according to my office files), of Oregon:

"Mr. F. was the first case treated by me. Had been stiff and unable to walk for several years. Nervous system run down. Administered doses as per directions. Noted improvement in three weeks' time. Health generally better; strength returning. A maximum dose of twenty-four minims [of Proteal No. 45] three times with good results. Gave him injections daily. Now he is able to walk without crutches with the assistance of some one to steady him." The treatment was given in association with the use of an electric baking apparatus.

Of similar tenor is a letter from physician number 232 (new series), of Arkansas:

"The hands—which were contracted so she could not extend them and could barely get a staff into each hand for walking—and the feet and hips were so stiff and sore she could not stand or move except with the two staffs in hand. She can now extend fingers, pain almost gone, and walks upright and has thrown away the sticks."

A little later the same physician made a brief formal report on his first four arthritis cases under Proteal treatment, which has added interest because the type of Proteal and the dosage employed in each case are specified:

Case 1.—Male age 60. Rheumatism of wrists and finger joints. Pain at night of an aching character causing considerable loss of sleep. These pains had been persistent and increasing for 10 years. Treatment began with six minims of mixed Proteals [No. 45—proteins of alfalfa seed, alfalfa meal, and millet seed] every other day, subcutaneously in forearms, increased injections gradually to twenty minims. Ten treatments given and cure resulted. No general reaction, but there was a marked local reaction with itching and stinging and marked cutis anserinus of about two inches surrounding the site of each injection that persisted about three days each time.

Case 2.—Rheumatic arthritis. Male age 58. Disease affects hands, elbows, shoulders, and hips. Could walk with difficulty by means of two staffs, one in each hand. Could barely open hands sufficiently to get staff (one inch in diameter) into hands. Tendons badly drawn and joints enlarged and very tender. Began treatment with six minims of mixed Proteals [No. 45, as above] every other day. No general reaction, slight local reaction. Increased the Proteals gradually to twenty minims. Gave in all twelve treatments, with marked improvement in all

joints. At close of last treatment patient could walk fairly well without any staffs and could open hands three-quarters of normal extension. This patient left the city and must be improving yet or he would report to me.

Case 3.—Mr. S. Age 48. Rheumatism of the fingers with deposits about joints, particularly about last joint of right index finger, to such an extent he could flex the finger but a trifle owing to a lump on under and outer side of the joint. Six to sixteen minims of mixed Proteals [No. 45] gave slow improvement until we were halted by a serious abscess at site of one injection. A rest of four weeks and then six injections of the rape seed Proteal [No. 42] on alternate days caused improvement sufficient for him to almost completely flex index finger. He is in much better health and comfort and frankly attributes relief to the treatment.

Case 4.—Mrs. M. Age 44. Chronic articular rheumatism of four years' duration, in feet and ankles, knees, hips, fingers, wrists, elbows, and shoulders. Had been bedfast several times; never much improvement. Suffered greatly with soreness, swelling, and tenderness of joints. Began with six minims of rape Proteal [No. 42], subcutaneously. Ached and hurt all night following first injection. Continued and increased the treatment every other day for two weeks, with steady improvement and no further reactions. After three weeks the improvement ceased and I changed to fifteen minims of alfalfa seed Proteal [No. 39]. A very marked improvement followed. Increased the alfalfa gradually to 25 minims. Four alfalfa injections were given, when she seemed almost entirely cured. At this time her son and husband were stricken with typhoid fever. She nursed and cared for both, until the husband died. During the four weeks of this unusual strain, she showed no return of the trouble, but to-day she returned with the report that she begins to have pains in the feet, ankles, and knees and they are somewhat swollen, and I have resumed alfalfa, 10 minims.

As representing an initial experience with Proteal therapy, this record of marked improvement of four consecutive cases of intractable character in the hands of a single practitioner is certainly enheartening. The aggregate number of such reports, giving tangible support to my personal experiences, is already notable. But in particular there come to me day by day informal letters from associated physicians that are often more stimulative than formal reports. For example, here is one that came to hand in this morning's mail from a physician out in North Dakota, with reference to a typical case of rheumatoid arthritis that has been under Proteal treatment for eight months.

"Mrs. — feels that the Proteal treatment is helping her, and

I can see an improvement, although the affected joints are still stiffened and sore. She rests much better and has not the constant pain that bothered her so much formerly. She is enthusiastic, and wishes to keep up the treatment faithfully."

Another recent letter, this time from British Columbia, tells that the patient, for fifteen years a sufferer from rheumatoid arthritis of the most intractable type, has just stood upon her feet for the first time in ten months, and has found a measure of relief from pain under Proteal treatment after she had long despaired of ever finding solace.

I would not be understood to imply, however, that Proteal therapy has hitherto proved adequate or satisfactory in all rheumatoid cases to which it has been applied. I have seen it fail in at least one case that came under my personal observation. The patient is a case of chronic arthritis, of progressive type, who twice came to my office for personal examination, and to whom the Proteals were administered in varying dosage for a term of months. On the morning on which I am completing this chapter, I received (from physician number 767, New York) the following letter:

"I regret to report that Mrs. — does not show any improvement under treatment with Proteals; I cannot conscientiously say there has been relief in any of the joints, while the cervical and lumbar vertebræ seem now to be involved. It is certainly an obstinate infirmity. Apparently in this particular case the Proteal does not seem to have developed any protection."

I may add that earlier reports suggest a certain improvement in general health, which, however, was not of vast significance; and that there were modifications of the blood count that led at one time to favorable anticipations. But apparently in this case we have failed hitherto to find the source of disturbed metabolism or to counteract effectively the pre-existing maladjustments.

In the contrast with this unsatisfactory showing, I may quote a letter from another physician concerning a case that also had come under my personal observation, but which, like the case just cited, was not treated personally by me, although in both cases the Proteals used were supplied from my laboratory. Here is the letter (from physician number 784, Montana):

"The patient whom you saw when you were lecturing on the Chautauqua Circuit has shown a remarkable improvement. All his friends speak about his ease in walking. Perhaps you do not recall, but he was suffering from chronic arthritis, and of some of the notables who treated him, Dr. — [a famous Chicago physician] was the last. The patient has attended two dances and taken an active part since beginning the Proteal treatment."

This patient, when I saw him, in August, 1917, did not attempt to rise from his chair. His arthritic involvement had been progressive, and had resisted all the conventional lines of treatment, including vapor and mud baths, change of climate, removal of the tonsils, and careful regulation of the diet under supervision of some of the most noted physicians in America. But improvement was immediate and almost spectacular under use of the Proteals, fifteen minims of Proteal No. 45 (alfalfa seed, alfalfa meal, and millet seed) being given as an initial dose. The letter from the physician above quoted was written after treatment had been continued about two months.

Three months later still a report from the patient himself tells that he had discontinued using the Proteals for about four weeks to see what the effect would be, and "although there was no distinct setback I notice that the swelling began to return gradually in my hand, and that my feet became more tender." Treatment was therefore resumed, with maximum dosage of about twenty minims, and the next report received (and the last one to date) states that the patient is "improving steadily."

In this case the results were so spectacular that they were known to every one in the community, and a considerable group of rheumatoid cases have been led to take the Proteal treatment. There are similar groups in various other communities, developed in the same way, but I shall not go into details regarding these or other cases. Full reports and an attempt at the statistical summary will be given in a book to be issued a little later under title, probably, of Proteal Therapy in Theory and Practice. Here I am concerned rather with the general interpretation, and the fundamental principles of the protein response. For the present purpose it suffices to have shown that in a certain number of cases administration of the Proteals has been followed by modifications of the rheumatoid condition of such character and under such circumstances as to leave it scarcely open to doubt that the administration of the protein had a causal relation to the observed favorable sequence of events.

Proteal Therapy and Asthma and Psoriasis

Before attempting a specific interpretation of the action of the Proteals in rheumatoid cases, in terms of the Proteomorphic Theory, I would refer to two other types of manifestation of disturbed protein metabolism, totally different in their localization, yet, in my opinion, having a certain ætiological relationship. I refer to bronchial asthma and psoriasis.

Both of these obstinate conditions have been treated, in a small but striking group of cases, with Proteals from my laboratory by associated physicians.

Our practical experience in the treatment of asthma with the

Proteals is exceedingly limited. Early in the year 1916 I received a letter from a physician who said that another California physician, a friend of his, having read an article of mine with reference to Non-specific Therapy had prepared and used the proteins of white of egg in treatment of his wife, who had asthma, with seemingly curative effect. I stated this fact to various physicians in the course of my lecture tour in the West during the summer of 1917, adding that there are some theoretical grounds for supposing that the use of the Proteals might be advantageous; notably, the fact that some physicians associate the asthmatic tendency with the rheumatoid condition, and that there is a certain amount of evidence associating asthma with protein infections, as in those cases that are susceptible to horse serum. The fact that the blood in many cases of asthma shows a pronounced increase of eosinophiles, if interpreted in the light of my own theories as the functions of this type of leucocyte, is corroborative of the idea of protein infection; the invasion being, according to my interpretation, conspicuously an invasion of unbroken protein molecules. Further suggestions along the same line are to be found in the obvious fact that bronchial asthma is itself allied to the spasm characteristic of acute anaphylactic shock from the introduction of a foreign protein into a vein, detailed reference to which was made in an earlier chapter of the present work.

Partly at least in response to my suggestions, a number of physicians have administered the Proteals to patients suffering from asthma, and the few reports that have come from them have been of the most encouraging and gratifying character. My brother, Dr. E. H. Williams, of Los Angeles, California, who has had very wide experience in the use of the Proteals in various affections, reports two cases of asthma that have yielded to the treatment and have reached a stage of seeming cure. The most spectacular case hitherto reported, however, is that of a patient in a city of the Northwest (Oregon), a dentist, who was subject to attacks of such severity that he had been obliged to discontinue practice of his profession.

Treatment consisted of the administration on alternate days of five minims of Proteal No. 45, containing in equal parts the proteins of alfalfa seed, alfalfa meal, and millet seed.

In reporting this case, the physician, who had had considerable prior experience with the Proteals from my laboratory and with whom I had seen a case of rheumatoid arthritis in consultation a few months earlier, wrote as follows, under date of November 8, 1917:

"I have a very severe case of bronchial asthma to which I have administered two doses of No. 45 with immediate and pro-

nounced relief. I wish to give him a regular course of the treatment."

Under date of December 22, 1917, he sent a personal letter containing this interesting item: "I want to tell you about the case of asthma. I used five minim doses of Proteal No. 45 every other day with the most striking results. Patient only experiences one or two slight attacks toward morning which soon pass off and he is free all day. Prior to the Proteal he was unable to do his practice (he is a dentist). At times I have gone into his office to find him stretched out fighting for breath. To show you how well he is feeling—he went duck shooting the other day and carried a sack of grain across the field to feed the ducks, with no effect whatsoever on his asthma."

And under date of January 17, 1918, there is this letter: "I wish to report further on the case of bronchial asthma that I have been treating with your Proteal. My results are most remarkable in that the case has resisted every other line of treatment for years. The patient had not had a whole night's sleep for three years to my personal knowledge. He reports to-day that he has been sleeping soundly for the last three weeks, and that he had no trouble whatsoever; gaining in weight; works at his profession every day, all day.

"I inject five minims of Proteal No. 45 every third day. I have not changed the type of protein."

Just a month later, February 17, the final report up to date states that the patient "is now using eight minims to a dose every third day, and is absolutely free from all symptoms of asthma while taking the Proteal that way."

I may add that the same letters that tell of the progress of this case also report on several cases of rheumatoid arthritis which "have all improved greatly, although the improvement has been much slower than in the asthma. I have used the same Proteal and the same dosage as in the asthma." Also there is report of a second case of asthma which is "steadily improving under the Proteal treatment. The asthmatic attacks are much less frequent, and on the whole she is getting better every day." This second asthmatic patient is the wife of a physician. Proteal No. 45 has been used in the treatment of this case as in the other.

I will here supplement this report in specific cases only by noting that the Proteals are now being tested on a series of asthma cases in a large city hospital by an associated physician who reports tentative results that are "really encouraging in practically every case." Ultimate conclusions from this elaborate test will not be reached for some time to come.

As to the treatment of psoriasis with the Proteals. It should

be noted that this is an application of non-specific protein therapy in which independent workers have priority. During the summer of 1917, however, a co-operating physician using Proteals from my laboratory treated several cases of psoriasis of long standing with striking success in every case. These were cases that had proved entirely resistant to antecedent treatment in the hands of leading Metropolitan skin specialists. The Proteals were administered in relatively small doses ranging from five to ten minims. To make the test definitive, there was no change in the diet of the patient, and no local application whatever was used. It was reported that in one case there was favorable change in the eruption in the course of ten days, but that the others showed no marked change for about five or six weeks; after which there were rather rapid and progressive modifications of favorable character, leading ultimately to complete disappearance of the eruption. Only one of the cases was seen by me personally, but this was a case in which the malady had been present for about eighteen years. The eruption had extended over the entire back of the patient at the time when the treatment was begun; and when I saw the patient about three months later the skin was perfectly smooth and free from any kind of eruption.

It is a familiar axiom of medicine that one case may prove nothing at all, and that a considerable series of cases may prove quite inconclusive or misleading when checked by more comprehensive experience. But when the cases under consideration involve maladies of such intractability as rheumatoid arthritis, asthma, and psoriasis, it would appear that such results as those above noted are at least thought-provocative. Certainly we are warranted in making further tests along similar lines; and I am glad to be able to report that tests are being made on a comprehensive scale that may be expected presently to justify more definite conclusions.

How Theory Explains Practice

Meantime a few words as to the theoretical ground on which an explanation of the possible utility of the Proteals in these conditions of disturbed metabolism may be based. The explanation will readily suggest itself to any one who has read the earlier chapters of this book attentively. In particular, it should be recalled that the therapeutic response to the administration of Proteals involves increase in numbers and (so it is believed) enhancement of the enzymic activities of the red blood corpuscles. This implies, further, according to the Proteomorphic theory, increased capacity of the organism to deal with

the end products of protein metabolism, and in particular with the purin bodies, hypozanthin, zanthin, and uric acid.

Notwithstanding the fluctuations of medical opinion on the subject, I believe that the uric acid hypothesis is still the most tenable thesis as to the underlying causation of the rheumatoid condition that has been put forward. But whatever the view as to this theory, there is practical unity of belief that the conditions under discussion are associated with disturbances of protein metabolism. Whether or not the purin bases are chiefly at fault, there is failure of complete and normal metabolism and elimination of the protein intake. The administration of the Proteals tends to normalize these processes. Very commonly the blood in these cases shows marked quantitative and qualitative abnormalities of the corpuscles. The Proteals tend to correct these abnormalities. Rarely indeed does the patient fail to improve in blood conditions and correspondingly in general clinical condition.

Through such modifica ions, in my belief, the therapeutic benefits of the Proteals are to be expected. I have never for a moment entertained the thought that the Proteals are specifics for the rheumatoid conditions. Indeed, I scarcely know what the word specific may mean in medicine except as applied to an agent directed against a particular type of microrganism. If any other use of the word be permissible, it might perhaps be justifiable to speak of the Proteals as specifics for the condition of anæmia, so direct and significant is the response of the blood-forming organs to their stimulus. But anæmia itself is, after all, a condition or symptom rather than a disease; and no wise physician would depend upon mere medication in treating anæmia, without giving thoughtful attention to its underlying causes, and endeavoring to remove these or modify them by eliminating sources of infection, counseling proper diet, and securing the co-operation of proper hygienic measures in general.

If this is true of the simplest anæmia, it is assuredly doubly true of the complicated anæmias that are associated with the various maladies of disturbed metabolism that are under consideration in this book. Above all, this is true about rheumatoid arthritis. This is a malady that makes its encroachments with almost diabolical persistency. It harks back always, I believe, to defective enzymic activities of the intestinal tract. As a rule, it is associated with life-long tendency to constipation. Its existence implies hereditary vulnerability of the joints, combined with inherited or acquired deficiency of action of the organs of digestion and assimilation, probably always associated with what for the patient in question are improprieties of diet. There is usually the history of the habitual ingestion of animal pro-

teins in excess. The use of coffee, tea, and cocoa may often be credited with an active share in fostering the condition.

One of my patients, now under Proteal treatment, affirmed that she had been exceedingly moderate in the use of animal foods and of tea and coffee; but presently mentioned that she habitually ate from a quarter to half a pound of chocolate each day and had been accustomed to do so for many years. It is probable that this quantity of chocolate would in itself supply purin bases enough to overwork a set of red corpuscles otherwise adequate. If this thesis is correct, it is obvious that to hope to benefit the patient greatly by Proteal or any other treatment without interdicting the use of chocolate would be like throwing water on a fire with one hand and kerosene with the other.

In leaving this aspect of the subject, however, I would again call attention to the fact that a very considerable number of cases are now on record in my office files in which patients suffering from rheumatoid conditions (and a smaller number of cases suffering from asthma and psoriasis) had proved resistant to every dietetic, hygienic, and medicinal procedure hitherto available, and yet have seemed to respond to the Proteal treatment so directly and so explicitly as to forbid the supposition that the observed improvement was only a coincidence. Coupling these observations with the theoretical considerations just presented, we are justified, I believe, in awaiting with a considerable measure of confidence the results of a more elaborate investigation as to the use of the Proteals in the treatment of rheumatoid conditions, asthma, and psoriasis.

Proteal Therapy and Tuberculosis

Another important malady that has been brought within the scope of Proteal therapy is pulmonary tuberculosis.

The first case of tuberculosis treated was of a character to subject the method to the severest possible test. The patient, a man about 35 years of age, had come back from southern California in a seemingly hopeless condition. Not only were lungs involved in the most critical manner, but the tubercular infection had spread to the larynx and had also involved two lumbar vertebræ. The case was so obvious that the diagnosis could have been made by any tyro, but in point of fact the advice of leading specialists had been sought.

The specialists had agreed in pronouncing an absolutely unfavorable prognosis. Nevertheless the patient showed a certain amount of response to tuberculin treatment. Recognizing the limitations of this method, however, as gauged by fairly wide

previous experience, it was decided, as a last resort, to test the proteal treatment, which hitherto had been applied only to cancer and two cases of rheumatoid arthritis; this decision being actuated by the observed effects of the remedy in regenerating the red corpuscles, on the seemingly plausible assumption that a remedy proved to have extraordinary powers to whip up the blood-forming organs must be of value in combating an anæmia of tubercular origin no less than the anæmias of cancer and rheumatism.

Accordingly the patient was placed under proteal treatment, early in September, 1915. The original Proteal extract was administered in the usual way, hypodermically into the arm, in doses of from 10 to 20 minims, given on alternate days.

The result was nothing less than spectacular. After the treatment was fairly under way the patient declared himself to feel a sense of exhilaration as if from taking champagne. He gained in weight, lost his cachetic appearance; cough and expectoration subsided. The bacilli disappeared altogether from his sputum, and physical examination of the chest gave evidence of the development of reparative processes. After treatment had continued for about three months improvement all along the line was so great that the most searching examination failed to reveal any evidence of active tubercular involvement.

On the 15th of December, 1915, an examination of the blood showed 90 per cent. hæmoglobin; 5,600,000 red corpuscles, and 8,400 white corpuscles, with 45.5 per cent. polynuclears, 35 per cent. large monocytes, 10 per cent. small lymphocytes, 4 per cent. eosinophiles, and 0.5 per cent. basophiles.

The patient's subsequent history was uneventful. The Proteal treatment was continued for a time, at lengthened intervals, and then there seemed no necessity for further treatment. The patient had gone to live in the country, and in the ensuing summer he was able to take part in rather active phases of farm work. He has a somewhat weak back, as a matter of course, from the former involvement of the vertebræ, but his general health and condition are highly satisfactory. On March 18, 1917, more than a year after discontinuance of the proteal treatment, the blood count showed 5,884,000 red corpuscles of normal type, and 9,400 white corpuscles. Obviously, there is scant suggestion in such a supernormal count of the tubercular condition, which had seemed to doom the patient until the proteal treatment was instituted. The patient's appearance and general condition accord well with the remarkable blood count.

Another gratifying case of pulmonary tuberculosis is that of a young girl of 22, whose progress has been so spectacular as to merit especial record.

The diagnosis in this case, as in the other, was absolutely unequivocal. The physical symptoms were typical: violent cough with profuse expectoration; temperature of 101, and pulse of 115; marked emaciation, and evident, even if not profound, cachexia. The rales were so conspicuous that they could be heard without the stethoscope and with the ear at a distance from the chest. Bacteriological examination of the sputum had been made, with positive findings, by the New York Board of Health. The patient's constitution was so undermined that her physician had told her she had but one chance in a thousand to live, and that chance contingent on immediate removal to the mountains.

Blood examination before treatment showed 3,954,000 red corpuscles, but 90 per cent. of these were misshapen or of the conformation that I am accustomed to speak as the sea urchin type. The bulk of the red cells was not at all commensurate with their number, since so high a percentage were misshapen. The white cells number 9,200, of which 78.5 per cent. were polynuclears, 11.5 per cent. small lymphocytes, and 9.5 per cent. large mononuclears, and 0.5 eosinophiles.

X-ray examination of the chest was made before treatment by a prominent roentgenologist, who reported as follows:

"There are numerous calcified glands in the lung lobes. In the right lung there are several calcified tubercles scattered from the base to the apex. Upper lobe is infiltrated, the infiltration being most marked around the proximal portion of the bronchial branches of the upper lobe. On deep inspiration there is tendency to fixation of the left diaphragm. The left auricle is moderately enlarged, and the right auricle and ventricle are moderately enlarged. Diagnosis, tuberculosis of the left upper lobe."

The administration of Proteal No. 45 (alfalfa seed, alfalfa meal, and millet seed proteins) was carried out in the usual way, beginning with 3 minim doses and increasing to 10 minims, administered hypodermically on alternate days. Changes in the patient's condition were immediate, striking, and highly gratifying. On the eleventh day of treatment it was recorded that temperature and pulse were normal; that the cough had almost disappeared, so that a sample of her sputum was obtained with difficulty; and that the patient's condition of general health had been so modified that she expressed a wish to return to her work. She had gained two pounds weight.

The blood count now showed 90 per cent. hæmoglobin, and 4,500,000 red corpuscles, not more than 10 per cent. of which were of the small, battered, misshapen type which made up the chief complement of cells before treatment. There were occasional normoblasts, and some groups of platelets. The white

cells numbered 9,000, with 77.2 polynuclears, 9 per cent. small lymphocytes, and 12 per cent. large mononuclears, 1.2 eosinophiles, and 0.25 per cent. basophiles. Thus it will be seen that the red cells had increased by 12½ per cent., the large polynuclears by 25 per cent., and the eosinophiles by 300 per cent. The activity of the blood-forming organs was further evidenced by the presence of a few lymphoidocytes and plasma cells. The white cells still showed some defect of staining quality, and a tendency to clump at the end of the smear; but, in general, the modification of the blood in so short a period was notable.

On the fourteenth day of treatment a second X-ray examination was made and the report was as follows:

"There is no evidence of an active process in the lungs. The diaphragm is freely movable and the area of increased density in the left upper lobe has disappeared. There is probably almost resolution of the area which gave signs of infiltration at the examination made twenty days ago."

Thus it appears that the X-ray examination confirms the findings of physical examination, which had shown the most striking modifications for the better, and is consonant with the observed modifications of the blood and the conspicuous change in the patient's appearance and general health. The further history of this case was absolutely uneventful. The patient continued to improve, and six months later she seemed entirely well.

As there had been no change of residence or modification of habits, and as no other treatment had been administered, it seems impossible not to ascribe the changes thus variously recorded to the hypodermic injections of the Proteal solution.

Such observations as these are obviously enheartening. It was natural that I should call attention to these cases in the medical addresses during my lecture tour of the summer of 1917; and it is perhaps not surprising that a considerable number of physicians were moved to make a trial of the Proteals in the treatment of tuberculosis. Reports of a very encouraging character have come from a considerable number of these physicians; and no single report in any way contraindicating the use of the Proteals in cases of tuberculosis.

Meantime my own personal office and consultation experience has been extended to a fairly representative group of cases of pulmonary tuberculosis at various stages of development. It would not be consonant with the plan of the present work to cite these cases in detail. A case that is fairly typical in its history and its response to treatment is that of patient Number 2,089, with pulmonary tuberculosis of fibroid type of ten years' standing. Usual history of forced feeding, temporary change of climate, and more or less steady progress in the wrong direc-

tion. Two hemorrhages in the past two years. Temperature never very high; seldom much above one hundred. Pulse 88 to 100. Hæmoglobin 70; red corpuscles 4,088,000, varying in size, with many microcytes; white corpuscles 14,000.

Treatment began with three minims of alfalfa seed protein (Proteal No. 39); continued on alternate days, increasing minim by minim until a dosage of ten minims was reached. A shift was then made for a few successive treatments to Proteal No. 60 (alfalfa seed and alfalfa meal proteins), one dose of which produced a rather severe local reaction, which did not recur with subsequent doses. After about three weeks of treatment a further shift was made to Proteal No. 45 (alfalfa seed, alfalfa meal, and millet seed proteins), beginning with five minims, and gradually increasing the dose to nine minims.

Throughout this period of treatment there was steadily progressive clinical betterment; a tendency of the temperature to approximate the normal (falling once to 97.4); and of the pulse to decrease from 98 and 100 of the earlier visits to 84, 80, and, in the course of six weeks, a fairly constant level of 72. Cough decreased, and character of sputum changed from thick and purulent to thin and whitish. The patient's color, appetite, and sense of well-being were conspicuously changed in a favorable direction.

Meantime there had been marked reduction in the quantity of albumen in the urine, which had been a complicating factor, and the blood count had shown a steady progression. On the twentieth day the red corpuscles, numbering 4,328,000, and the white corpuscles held at 14,000. On the tweny-eighth day the red corpuscles numbered 4,704,000, and the white corpuscles 13,600. On the forty-third day the red corpuscles numbered only 4,304,000, but were large, round, normal-looking for the most part, very few of them tending to take the purple stain, as many of them had on a previous examination; and the white corpuscles had dropped to 8,000. On the sixtieth day the red corpuscles numbered 5,168,000, one-third of them remaining smooth and normal-looking after two hours in the counting chamber, and another third of large size, though crenated. A fair proportion of the red corpuscles remained large and fairly smooth after twenty-four hours in the Toisson fluid. The white corpuscles, stained for the most part of a fairly pale, opal blue in this fluid, numbered only 9,000.

Taken in connection with the clinical symptoms, this blood count of the sixtieth day showed the corpuscles in virtual command of the mixed infection. An earlier examination had shown a marked reduction in the tubercle bacilli, only one or two remaining to the field. It now seemed desirable to minimize the total quantity of protein introduced hypodermically, while main-

taining or accentuating the impulse to the blood-forming organs, and it was thought that this might be accomplished by using small doses (three or four minims) of Proteal No. 65, a combination of the proteins of alfalfa seed, alfalfa meal, millet seed, rape seed, and mustard seed.

Such is the standing of the case at the moment of the present writing: Temperature and pulse normal; blood conditions all that could be desired; cough and sputum favorably modified; kidney complications minimized; patient's skin with healthy glow; blood pressure 110; conspicuous physical and mental buoyancy.

It is perhaps of interest to add that this patient had at the outset a slight hyperthyroid complication, the right lobe of the thyroid gland being conspicuously enlarged. The rapid pulse and a certain nervous hyperæsthesia were no doubt in part associated with this condition. As an auxiliary to the Proteal treatment, the patient was given one to two drops of a saturated solution of potassium iodide three times daily for five or six weeks, at the end of which time the gland had been reduced to normal size. No other internal medication of any kind was employed. There had been from the outset a modification of diet, however. As is my custom with all cases suffering from protein intoxication, whether or not of bacterial origin, I had placed the patient largely on a vegetable and milk diet. The building up of the red cell count and improvement in quality under Proteal treatment, associated with the cessation of forced feeding with meat and eggs, is an observation that has been duplicated in many other cases not only of tuberculosis but of various other asthenic conditions, including cancer. The theoretical explanation is that proteins in large excess overtax the red corpuscles (in the handling of the end products), and increase the anæmia they are supposed to combat. But on the other hand the protein intake must not be cut too low. The nitrogen balance must be maintained.

While repeating that I make no attempt here to present, even in summary, the total experience in the treatment of tuberculosis with Proteals, I cannot refrain from presenting very condensed histories of a small group of cases under treatment by an associated physician in the State of Washington, who, as a result of these preliminary observations, now has under Proteal treatment a large group of cases of tuberculosis of which records will ultimately be available. The condensed reports of the three cases to which the Proteals were first administered are as follows:

(1) Mrs. K. B., 56, Pulmonary tuberculosis. Involvement of upper half of right lung and upper one fourth of left lung. The Proteal treatment began with two and a half minims of No. 45,

increasing one-half minim every other day until seven minims were given; then dose every fifth day, seven and one-half minims per dose. Still on Proteal No. 45, fifteen minim dose. Result after ninety days: Reduction in temperature from 103-104½ to 99-100½. No more night sweats. No cough. Increased appetite and weight. Hæmoglobin increase to 90 per cent., red corpuscles to 4,200,000. Considerable fibrosis of both lungs.

(2) Mrs. H. F., age 35. Pulmonary tuberculosis with pleurisy, two years' standing, left side. Involvement of apex of right lung and entire left pleura. Proteal treatment began with four minims No. 45, increasing one minim every third day till seven minims were given; then repeating same dose every five days for three to four doses before increasing dosage one minim again. Still on Proteal No. 45, fourteen minim doses. Result after ninety days: Right apex clear of rales, moisture, and all symptoms of infection. One-half left pleura clearing up. Reduction of temperature, gradually, from 102-103½ to normal. Increased appetite. Able to lie on left side for the first time in two years. Blood picture improved to nearly normal. All symptoms improved.

(3) Mrs. C. D. E., age 20. Pulmonary tuberculosis. Both upper lobes involved. Proteal treatment began with three minims No. 45, increasing one minim every other day till eight minims were given; then the same dose every third day for three or four doses, after which the dose increased one minim, etc. Result of treatment after ninety days: Temperature normal. Cough decreased. Blood picture same as before treatment.

Such observations as these are certainly stimulative. I have in hand a considerable body of similar testimony from physicians in various parts of the country, and fresh evidence comes to me week by week. The experience of these associated physicians, coupled with my personal observations, appears to me to justify the hope that in the Proteals we have new weapons to aid the physician in coping with a malady which, although measurably checked in onslaught in recent years, still has a mortality rate of about 145 per hundred thousand population—a malady of which, otherwise stated, claims about 145,000 victims in a year in the United States alone and not far from a million in the civilized world.

It will be understood, of course, that no suggestion is made that the Proteals exercise a specific function in combating the tubercular condition. Their action here, as elsewhere, is directly on the blood-forming organs in accordance with the fundamental principles of antigenic response. But the secondary effect on the intruding protein masses constituting areas of infection in the lungs or elsewhere is so natural a consequence that it might

have been expected, and was in point of fact predicted by me as a probable sequel—a prediction of so definite and tangible a character as to have led to the original clincal tests above described, and, sequentially, to the more comprehensive tests that are now under way in various sanitariums and hospitals and in the hands of a large number of private practitioners.

In an earlier section of this book I have called specific attention to the similarity of the blood conditions in advanced cases of tuberculosis and of cancer. I would reiterate here the not altogether unfamiliar doctrine that the tubercular subject does not as a rule die of direct poisoning by the tubercle germ, but of secondary infection associated with other types of micro-organisms, and with the ultimate development of degenerative protein-product masses in the lungs or elsewhere, partial hydrolysis and absorption of which produces a toxæmia strictly comparable to the toxæmia of malignant neoplasms.

There was every *apriori* warrant, therefore, for the prediction that the blood corpuscles might be stimulated by protein therapy to do something toward proteolizing and eliminating from the system the obnoxious protein masses that owed their inception, to be sure, to the original invasion of the tubercle bacillus, but which have now become in effect malignant neoplasms; totally different, assuredly, from the masses usually classified as cancerous in their histological structure and in the specific type of irritant associated with their genesis; yet fundamentally akin to cancer in that their development was conditioned on relative failure of the corpuscular activities, and in their inherent tendency to engender progressive exhaustion of the blood-forming mechanism and ultimately to terminate the life of the individual in whose body they develop.

The analogy of the observed effect of Proteal treatment of cancer, therefore, gives additional support to hopeful prognostications as to the value of the Proteals in tuberculosis, founded theoretically on the Proteomorphic theory and practically on observation of a limited number of very striking cases hitherto subjected to this treatment. By the time my projected book on *Proteal Therapy* is ready for the press, there is every prospect that a body of evidence will be in hand that will answer unequivocally the question as to the ultimate value and the limitations of Proteal Therapy in its application to tuberculosis.

Meantime, in order to round out this preliminary survey of the present status of the method, we may now turn to a consideration of the use of the Proteals in those conditions of blood disturbance in which the ætiological factors are so obscure that the blood conditions themselves have taken rank as specific maladies under the name of anæmias and leukæmias; in the antagonizing

of which conditions the Proteals exercise so direct a function that here, if anywhere, their action might be said to be specific. In making this survey, however, I shall constantly have in mind the thesis that the anæmias and leukæmias are, in the last analysis, secondary conditions; the so-called primary anæmias being, in my belief, usually associated with conditions of intestinal toxæmia, and being therefore inseparably linked with the other conditions of disturbed protein metabolism that have all along engaged our attention. The word anæmia is after all only a convenient name for a condition that is a necessary precursor or concomitant of all types of chronic toxæmia. For the moment, however, we are to focus attention on the blood conditions themselves, and to view from a slightly new angle the effect of the Proteals in dealing with these disturbed conditions.

Intestinal Toxæmia and the Anæmias and Leukæmias Under Proteal Treatment

In the *Monograph* of December 1, 1916, I gave a brief preliminary account of an interesting case, in which there was chronic protein (intestinal) toxæmia in which the red cells had the qualitative features of pernicious anæmia, although not reduced in numbers as in full development of that malady; and in which there was pronounced leucocytosis, with embryonic (ontogenetic) types of cells suggesting a leukæmic tendency.

A typical count before treatment showed 3,850,000 red cells (crenated, vacuolated; anocytosis; poikilocytosis, pronounced chromophilia; normoblasts, megalocytes); very few platelets; and 57,000 leucocytes, with 70.6 per cent. polynuclears (full cytoplasm, feebly granular, non-acidophile); 21.6 lymphocytes (mostly small and very basophile); 5.4 per cent. large mononuclears (one-third lymphoidocytes); 2.6 per cent. eosinophiles.

After six days of Proteal treatment (four doses of 4 to 8 minims, hypodermically into arm), red cells advanced to 5,012,000 in number and much less abnormal in appearance; normoblasts exceedingly rare, some groups of platelets; number of white cells reduced to 5,100, with 51 per cent. polynuclears, 30.5 per cent. small lymphocytes, 14 per cent. large mononuclears, 2.5 per cent. eosinophiles, and 2 per cent. basophiles. Patient's general condition and subjective symptoms very markedly changed for the better, as might be expected.

This case appears so remarkable, that I perhaps cannot do better than to use the record of its blood modification as a text to guide the brief but explicit study of this aspect of the subject. Of course it is not to be overlooked that very sudden changes in the blood count, and even in the quality of the cells, may occur

spontaneously—the word spontaneous being of course merely an expression of our ignorance—in cases of pernicious anæmia and leukæmia. But in the present instance, the patient had been under observation and under treatment of the conventional type for a long period before Proteal medication was resorted to, and we are justified, I think, in feeling a certain measure of confidence that the blood changes noted were the result of the administration of the vegetable proteins, and not merely an accidental concomitant of such administration. In any event, it will be of interest to follow the subsequent history of the case before attempting the promised interpretation of the observed phenomena.

Briefly summarized, the record is as follows:

Between the sixth and eighth day (following the record above given), the patient was in the country and had no Proteal treatment. She had departed somewhat from the established dietetic regimen, among other things eating sausage. On the eighth day she suffered a clinical relapse. Her head became heavy, and throbbing. Her ear rang intolerable. She had no appetite. Her mental condition was depressed and apprehensive. These were among the symptoms that had characterized her malady all along. The nausea and vomiting that had also characterized it did not recur on this occasion. The blood count now showed 4,384,000 red corpuscles, with numerous normoblasts and free microblasts, and abundant platelets. The white count had advanced to 12,800, including large numbers of small lymphocytes of such diminutive size as to be recognized with difficulty except under high powers of the microscope. The differential count showed 15 per cent. polynuclears, 32 per cent. small lymphocytes, 8 per cent. large monocytes, and 2.6 eosinophiles. Thus there was a tendency to increase in polynuclears, a very marked increase of small lymphocytes, and a reduction in the large mononuclears. More than half of the large mononuclears were neutrophile myelocytes.

Proteal treatment was at once reinstated, the particular protein used on this occasion being an extract of rape seed (No. 42). On the eleventh day the red cell count showed a marked falling off, being reduced to 3,708,000. The general aspect of the red cells was, however, much more satisfactory than at the outset. Meantime the white cells were now 6,960. The differential count was highly satisfactory, showing 50.7 polynuclears, 28.5 per cent. small lymphocytes, 18.5 per cent. large mononuclears, and 2 per cent. eosinophiles. Of the large mononuclears, about 30 per cent. were typical large monocytes and 30 per cent. large lymphocytes, and 40 per cent. neutrophile myelocytes. As heretofore, the polynuclears tended to stain a rather pale light blue, but the tendency to clump was not conspicuous as at the outset.

The patient's physical condition was much better than on the eighth day, but not so good as on the sixth.

Proteal treatment was continued, in doses of 5 to 10 minims, on alternate days, and the clinical progress of the patient was so conspicuous as to be noticed by all her friends. She spoke of herself as being "quite made over." The distressing giddiness disappeared altogether; her appetite was good, and she had no nausea or other gastric disturbance; she slept well, felt cheerful and bouyant, and in general was in a condition that simulated normal health. On the 28th day of the treatment, her blood count showed 4,074,000 red corpuscles of fairly normal appearance (totally different in aspect from the original condition), and 7,150 white corpuscles, of which 52 per cent. were polynuclears, 28 per cent. small lymphocytes, 18.5 per cent. large mononuclears, and 1.5 eosinophiles. The polynuclears stained blue, but their cytoplasm was distinctly acidophile. The mononuclears were mostly typical large monocytes, with only a few questionable myelocytes. No normoblasts were seen, but there was a fair number of platelets. Except that the red cells were not quite as numerous as might be desired, this blood picture is in the highest degree satisfactory.

On the 35th day, the defect in the red corpuscles had been remedied, as these now number 5,328,000. The quality of the red cells was correspondingly satisfactory, being recorded in the main very normal, except that some were small. The white cells now numbered 7,700, with 63.5 per cent. polynuclears, 13.5 per cent. small lymphocytes, 19 per cent. large monocytes, practically all of them large lymphocytes or typical large monocytes, 2 per cent. eosinophiles, and only a negligible number of myelocytes. It is recorded that the polynuclears were of normal appearance with cytoplasm taking acidophile stain moderately, and nuclei staining deeply. Large monocytes and eosinophiles were large and beautifully typical.

Here it will be noted that the polynuclears were more numerous than in the preceding counts (although far short of their original percentage), and that this increase had apparently been made at the expense of the small lymphocytes, the large mononuclears being more abundant than on any previous occasion. That this blood condition was salutary is evidenced by the fact that the patient's clinical condition continued in the highest degree satisfactory, notwithstanding that she had been for ten days of this period under excessive mental strain owing to the critical illness of a member of her family. It now became necessary for the patient to go to California, and she accomplished the journey without incident, although she would have been utterly

unable to undertake such a voyage six weeks earlier, before beginning the Proteal treatment.

At the end of the journey, the patient was subjected to both mental and physical strain for a term of weeks, during which time she had only occasional doses of Proteals, and was not under observation as to the blood count. It was reported that she stood the strain amazingly at first, but subsequently, after four or five weeks, suffered a relapse, with recurrence of spells of dizziness and a feeling of general debility. Proteal treatment was resumed, and continued with clinical benefits, after the patient's return to New York, No. 45 being chiefly used, in doses of five to eight minims, administered at lengthening intervals, and finally discontinued about six months after the initial treatment.

On March 30, 1917, the blood picture was: Hæmoglobin, 90; red corpuscles, 5,152,000; leucocytes, 5,000, with 56 per cent. polynuclears, 18.5 small lymphocytes, 24 per cent. large monocytes, and 1.5 eosinophiles. On May 16, the count showed 4,744,000 erythrocytes and 5,600 leucocytes. Seven months later (December 11), with no treatment since June, the blood showed 4,912,000 red cells and 6,000 white; and on January 28, 1918, fourteen months after the original use of the Proteals, the examination showed 5,528,000 red cells and 8,600 leucocytes.

Clinically, the patient has attained a condition of fairly robust health, all the disturbing symptoms having disappeared; and such is her condition at the moment of present writing, sixteen months after the institution of the Proteal treatment and eight months after it was discontinued.

It is worth while to make inquiry as to whether a satisfactory theoretical explanation can be found of such striking modifications of the blood count as are above recorded, in particular with reference to the spectacular decrease in the number of white corpuscles at the outset. It should be added that I have had no closely similar case with equally marked leukæmic tendency in which so spectacular an effect was observable; but, on the other hand, I have numerous records, some of which have already been presented, of cases in which the white blood cell count has been very rapidly reduced from 12,000, 14,000, and 16,000 to the normal by a few doses of vegetable proteins. How shall we account for this striking phenomenon?

Blood Changes Tentatively Explained

It is desirable to say that the explanation about to be given is put forward tentatively. We know too little about the genesis and transformations of the blood corpuscles to speak dogmati-

cally on this aspect of the subject. Nevertheless, I think that data are sufficient to enable us to suggest at least a plausible hypothesis as to the *modus operandi* of white cell decrease or modification in direction of the normal under Proteal treatment. A clue to the explanation is to be found, it seems to me, in the complementary or compensatory relation that exists between the white and the red corpuscles. All theories aside, it has long been known that when there is sudden reduction in the mass of the blood, through hemorrhage, a rapid leucocytosis supervenes, it being apparently a more facile matter to increase the leucocyte population than to bring the red corpuscles back to normal numbers. The difference in bulk between the two perhaps explains this more or less adequately, it being recalled that the red cell population is normally from 500 to one thousand times the census of the white corpuscles. It will be recalled, also, that under normal conditions there is a far wider range of variation in the number of white corpuscles than in the red. A normal postprandial leucocytosis may increase the numbers of white corpuscles by 50 per cent.; and, contrariwise, a corresponding reduction takes place a few hours later. No such oscillation as this occurs under normal conditions in the red cell population.

If the post-hemorrhagic leucocytosis be accepted as in a sense compensatory, it must be assumed that the leucocytes are able to some extent to perform the work of the red corpuscles. Speaking in terms of the Proteomorphic theory, we may assume that there is no absolutely fixed line of demarcation between the proteolytic activities of the white corpuscles and red. (I shall present below the record of a case of leukæmia, that strikingly emphasizes this view.) The theory assumes that the red corpuscles are incapable of dealing with the full-sized protein molecule, and that the white corpuscles cannot adequately care for the later products of hydrolysis, of the polypeptid order. But in all probability there are intermediate stages at which the activities of the two sets of corpuscles overlap. It is conceivable, for example, that both the white corpuscles and the red may be able to deal more or less adequately with molecules at the peptone stage, and that the white corpuscles may hand the material over, so to speak, to the red corpuscles at somewhat variant stages of decompounding under different conditions.

If we assume, as was done in the Proteomorphic theory, that the disruption of the white corpuscle and the consequent liberation of its contents takes place as the result of osmotic pressure, and that this pressure is due to the decompounding of the protein molecules within the substance of the leucocytes, it is at least conceivable that the stage of decompounding at which disruption will occur is dependent in a measure on the quantity of protein

which the white corpuscle has ingested. It will be recalled that, according to Van't Hoff's theory, each individual molecule, whatever its size, presses with equal force in a liquid medium. If, then, in a given case, a leucocyte has ingested a large quantity of protein, the decompounding of this protein might produce a sufficient number of molecules, at, let us say, the proteose stage to exert a disruptive force on the leucocytic membrane; whereas, had the amount of protein originally ingested been smaller, decompounding to the peptone stage might have been necessary before an equivalent pressure was exerted.

If this suggestion be accepted, it follows that, given a fixed quantity of protein papulum in the blood, the larger the number of leucocytes the smaller would be their average intake of protein, and hence the more complete the average stage of decompounding before disruption. In other words, the larger the number of leucocytes, the more efficient their work as protein hydrolyzers. Where a small number of leucocytes must have turned over their product to the red corpuscles at the peptone stage, a larger number of leucocytes may reduce it all to the polypeptid stage, and thus, seemingly, conserve the resources of the red corpuscles by limiting the work put upon them.

If such are indeed the relations of white and red corpuscles, and the hypothesis just suggested be accepted as plausible, a high leucocyte count such as that recorded in the case of the patient above reported (57,000) must be accepted as a salutary attempt on the part of the organism to compensate for the inadequacy of the red corpuscles, indicated not only by their small number (3,850,000) but also by their extreme defects of size and quality. This was a case, seemingly, where chronic intestinal defects of secretion of the digestive enzymes (pancreatic, biliary, or enteric) persistently led to the introduction into the blood of protein products not hydrolyzed to the normal polypeptid or amino-acid stage. This put an incessant strain on the red corpuscles, which probably (could the full history of the case be known) were for a time increased in number, but which ultimately, owing to exhaustion of the blood-forming mechanism through long subjection to the same toxin, became decreased in number and utterly dyscrasic in quality.

Then came the increase of white corpuscles to endeavor to compensate the defects of the red cells. The white cells would accomplish this, according to hypothesis, by handling as effectively as possible the larger protein molecules normally or abnormally present in the blood. If, however, the intermediate and later products of hydrolysis continue to intrude themselves in excessive quantities, the strain on the blood corpuscles would be cumulative, and even though the white corpuscles were pro-

duced in larger and yet larger phalanxes, disaster must in the end result, since no quantity of white corpuscles could compensate altogether for the lack of reds, inasmuch as the red corpuscles alone are capable of dealing with the end-products of protein decompounding.

The time would come, apparently, when the increase of white corpuscles passes the point of maximum efficiency, the amount of protein papulum for each being so small that a relatively long life is vouchsafed to each white corpuscle before its contents reach the stage of disruptive pressure. There would then be an accumulation of old white corpuscles in the blood, piling up ultimately in such numbers as to produce the enormous counts familiar in advanced stages of leukæmia.

On the other hand, under such conditions, the protein content of each individual white corpuscle would, on the average, be reduced to an exceedingly low stage of hydrolysis, that is to say, to the lowest stage to which the leucocytic enzymes can reduce it; and, on disruption, the leucocytes would supply the red corpuscles with, let us say, polypeptids (perhaps dipeptids or monopeptids), making the smallest possible requirement on their enzymic activities. Should something take place that would cause the disruption even of the major part of the white corpuscles in a brief period, the amount of toxicity to the nervous system that would result would depend entirely on the equipment of red corpuscles. Moreover, it is not impossible that when the red corpuscles are abundant, their enzymes may have a catalytic effect on the white corpuscles, stimulating them to greater enzymic activity, and thus facilitating their disruption. That some such complementary relation between the red corpuscles and the white exists, might reasonably be expected, similar adjustments between organs of complimentary function being familiar throughout the organism. An agent which stimulated the production of increased members of red corpuscles, or one that increased the enzymic activities of these corpuscles, would thus, secondarily, result in effecting the more rapid decompounding of the white corpuscles, thereby reducing their number.

I am disposed to think that this line of reasoning explains the rapid decrease of white corpuscles in the case above cited. It will be recalled that coincidentally with this decrease in white corpuscles there was an increase of red corpuscles from 3,850,000 to 5,012,000,—an increase, in other words, of more than 30 per cent. The size and quality of the individual corpuscle were more than correspondingly enhanced, so it may plausibly be assumed that the enzymic capacities and activities of the red corpuscles as a whole were measurably doubled. The increased red cell enzymes stimulating white cell catabolism, and the red cells now

being adequate to deal with the end-products of protein hydrolysis thus liberated, the excess accumulation of white corpuscles would be immediately done away with, and the mother cells of the leucocytes, being no longer stimulated to excessive activity, might resume their normal rate of functioning. Indeed, it is consistent with what has been suggested, to assume that in such a case as the above, where leukæmia had not been far developed, the leucocytic mother cells had not acted with extreme prolificness, and that the large leucocytic population was due, in large measure, to accumulation rather than to over production.

On these assumptions, the only mystery connected with the matter would be the fact of the extraordinary regeneration of the red cells themselves under influence of the Proteal remedy. This is to be explained, according to the Proteomorphic hypothesis, as taking place in connection with the following sequence of events: (1) the vegetable protein introduced hypodermically is quickly absorbed into the blood stream, where (2) it encounters a multitude of white corpuscles that quickly ingest it and effect its partial proteolysis. Disruption of the white corpuscles taking place through osmotic pressure, the polypeptids to which the vegetable proteins have been reduced (circulating now freely in the blood) come in contact with the mother cells in the marrow with the effect of an altogether new stimulus. These cells, by hypothesis, have become exhausted to the stimulus of the protein products that come to them through the intestines, and are performing their functions very inadequately. Now, however, they respond to the new impulse with alacrity, and put forth a new generation of red corpuscles totally different in quality from those that have been their recent progeny. These new cells are able to deal with the end-products of protein catabolism already in the blood, and with any new increment that may come; and there is possibility of a re-establishment of normal conditions of metabolism.

If, now, the patient is placed under proper dietetic restriction, so that the faulty intake of protein products is in a measure corrected; and if the Proteal injections are continued day by day, so that the blood-forming mechanism receives a continuous stimulus, conditions are favorable for a permanent regeneration of the blood, and for the clinical cure of the patient.

Such, as I see it, is a plausible explanation of the manner of action of proteantigens in effecting the transformations of the blood that have been so frequently observed, of which the case above recorded furnishes an extreme instance.

If this explanation be accepted, it will be clear that the same line of reasoning applies to any and every type of protein intoxication. Intestinal toxæmia and cancer are obviously very differ-

ent conditions (though I venture to doubt if the latter ever exists without having been preceded by the former), yet the effects on the blood and on the system at large of protein products absorbed through the intestines and of those liberated from cancer tissue may be substantially identical. (The high glutamic acid contents of tumors is worth recalling in this connection.) It is an observed fact that many diverse conditions, including intestinal toxæmia, tuberculosis, and cancer, may bring the blood to seemingly the same stage of abnormality, characterized by red cells reduced in number and of the pernicious anæmia type, and by leucocytes increased in number by way of compensation, with relative neutrophilia. It is not strange, then, that the same line of treatment may be applicable to all these conditions—and to numerous other conditions similarily characterized by disturbed protein metabolism—since the fundamental maladjustments are the same in all.

If a fairly satisfactory explanation may thus be found of the increase of red corpuscles and the decrease of leucocytes under Proteal treatment, as in the case above cited, it must be admitted that an explanation of the striking modification of the differential leucocyte count is not so readily forthcoming. Nevertheless, it is possible to offer at least a provisional explanation, along the lines of an hypothesis of differential leucocyte action presented in an earlier section. In examing this hypothesis, we shall have occasion to consider the blood modifications in an interesting case of leukæmia, already once or twice referred to. For the moment, however, attention is directed to the modified leucocyte count in the case of anæmia already discussed. It will be recalled that the polynuclears at the outset numbered 70.6 per cent of the total leucocyte; and that after a few days' treatment their proportion was reduced to 51 per cent. Meantime, the small lymphocytes had increased from 21.6 per cent. to 35 per cent., and the large mononuclears from 5.4 per cent. to 14 per cent.

This would appear to tell either of a disproportionate destruction of mononuclears or of a no less disproportionate production of mononuclears. And the problem thus presented does not apply to this case merely, for I have posited a similar modification of the differential count as a characteristic response to protean-tigen treatment. Reference to this has been made many times in the preceding pages; and tables demonstrating the modification in series of cases are presented in the cancer *Monograph*. What is the explanation of this modification?

Perhaps the simplest explanation of the change of polynuclears would be that the hydrolytic function of this type of leucocyte is most directly compensatory of that of the red corpuscles. It

was suggested above that the polynuclears deal with the proteins at approximately the peptone stage, carrying hydrolysis to a stage that fits the protein products for the purposes of the red corpuscles. On this assumption, it is logical to suppose that as the red corpuscles are overworked, neutrophile recruits may be called out to make sure that the largest possible proportion of proteins in the blood is reduced to the polypeptid stage, thus relieving, as far as may be, the strain on the red corpuscles.

It was noted, however, that the polynuclears unquestionably had to do with resistance to bacterial invasion; and it was further suggested that they perhaps have to do with the decompounding of fats. These suppositions obviously introduce complications, which must be borne in mind, but which do not call for more elaborate consideration at the moment; inasmuch as, in the case under consideration, there was no acute bacterial invasion in question, nor any sudden modification in diet on one hand or the patient's weight on the other suggesting a change in the needs of the organism as regards fat metabolism. Yet there was apparently a very sudden modification in the systemic need of polynuclear leucocytes. This modification was associated with very marked increase in the numbers, and presumably in the efficiency of the red corpuscles; and a corresponding increase in numbers and presumptive activities of the mononuclear cohorts.

Viewing the matter with reference to these two essential modifications, the thought obtrudes itself that when mononuclear leucocytes on one hand and red corpuscles on the other are working at maximum efficiency, their joint hydrolytic activities cover the entire range of protein catabolism, leaving the polynuclears free for the auxiliary tasks of combating bacteria (with their large lipoid content) and handling fats in general; possibly, also, having to do with the catabolism of carbohydrates,—the latter possibility, however, being mentioned here only parenthetically, as I have purposely refrained from complicating the problem by reference to this group of alimentary constituents.

Elaborating the view just suggested, we may assume that the large mononuclear leucocytes begin the hydrolysis of proteins; and that the small mononuclears, when working at maximum efficiency, carry it forward to the stage of adequate preparation for uses of the red corpuscles, which ultimately complete the work of decompounding; and that in proportion as this simplified method of handling is perfected, the need for the services of the polynuclears in this connection is minimized.

That this would represent to some extent a conservation of bodily energies is suggested in the relative complexity of organization of the polynuclears. Seemingly the mononuclears are cells

of a more primitive type; calling for less expenditure of energy, therefore, in their development.

It will be obvious that there is nothing inconsistent in all this with the hypothesis of differential leucocyte functions already put forward. The present view is merely an elaboration and extension of that hypothesis. It has been urged all along that there is probably a considerable range of variation or latitude as to precise proteolytic functions of each type of corpuscle.

This is no more than is observed everywhere in the organism; the possibility of vicarious functioning being a necessary safeguard to health and to life itself. Thus we find that there is no single organ that has absolute control over any stage or phase of food digestion in the alimentary tract. There are more or less compensatory functions between salivary glands and pancreas, and between stomach, liver, and the enteric walls. Even the highly specialized functions of the kidney are in a measure duplicated by the functions of the glands of the skin. Moreover, two kidneys are provided, although a single kidney is amply competent under ordinary circumstances to meet elimination requirements. Similarly there are two lungs, providing an aggregate alveolar surface vastly in excess of the maximum needs of the organism.

It is not strange, then, that the corpuscular cohorts should show a similar margin of safety; and we need not be surprised to observe that, under exceptional circumstances, metabolic conditions apparently approximating the normal may be maintained when there has been a profound disturbance of the observed normal conditions of the corpuscles,—just as a person with one kidney or with one affected lung may appear to retain a normal level of health; or, to make a still closer analogy, as a patient may be maintained for a considerable period by rectal feeding, the functions of the normal digestive glands being for the moment abrogated. I have just had report of such a case where (owing to a gastric ulcer) rectal feeding has been the sole method of alimentation for a period of more than ten months.

A Case of Leukæmia

I am led to emphasize this aspect of the subject because of certain anomalies forced on my attention by the case of lymphatic leukæmia to which reference was above made. The patient, a man of 65, is known to have been leukæmic for several years. When the patient first came to me for examination, he brought with him the report of a blood count made two years earlier which showed 200,000 leucocytes. No blood examination had been made in the interval, but my examination revealed upward

of a million leucocytes to the cubic millimeter, with red count not far above three million; the smear showing the leucocytes to be small compact lymphocytes almost exclusively.

The clinical symptoms that led the patient to come for treatment consisted chiefly of extreme enlargement of glands at each side of the neck, in the region of the parotids; enlargement of lymphatic glands at the back of the neck and head, in the axillary regions and inguinal regions and elsewhere; associated with severe pains, particularly located in the region of the enlarged glands at the back of the neck and head.

The patient was placed under Proteal treatment, the mixture of the proteins of alfalfa seed, alfalfa meal, and millet seed (Proteal No. 45) being administered in doses of from three to eight minims on alternate days; a shift being subsequently made to rape seed protein (Proteal No. 42). There was a very prompt response, in that general reduction in the size of the enlarged glands took place. The glands at the sides of the neck were reduced so markedly as to alter the patient's appearance very noticeably. The lymphatic swellings at the back of the neck and head, and in axillary and inguinal regions were greatly reduced in size or altogether disappeared. The pain, which had been persistent, disappeared and has not recurred. Nor has there been any tendency to return of the glandular enlargements, except that a temporary swelling appeared in each mastoid region following an attack of influenza (shortly after convalescing), which swelling the patient ascribed to "catching cold" through sitting in a draft.

I shall not go further into the clinical details of this patient's history in the present connection. We are here concerned with the blood conditions, which are of the most striking and (in connection with the clinical state), even mystifying character. After two weeks of Proteal treatment, there was a very marked modification in the character of the leucocytes, in that large number of cells appeared which were two or three times the size of the prevalent lymphocytes, and which took the stain much more faintly, and appeared somewhat vague and ragged in outline in contrast with the sharply rounded, bullet-like lymphocytes that clustered everywhere so thickly as to remind one of grapes on the vine. These large cells could not well be classified other than as large monocytes, although only by rare exception could one be found that showed a distinct nucleus and dark-stained cytoplasm. In general these large cells, like the small lymphocytes, showed no cytoplasm whatever. They appeared to be all nucleus, with vague boundaries. They gave one the impression of lying in the background as it were, and at a different level, from the protruding grape-like small lymphocytes. The red corpuscles,

meantime, tended to take a coppery stain. Many of them were conspicuously vacuolated, and a few showed faint neuclei.

But whereas the mononuclear leucocytes of these two very distinct types sprinkled every field of the microscope so thickly as almost to compete with the red corpuscles, it was necessary to search across a large number of fields in succession before finding a single polynuclear. Now and again, however, one did appear; and the character of this rare exhibit was altogether unequivocal. The nucleus was usually of bizarre type, but distinct and clearly defined; and there was a normal quantity of clear cytoplasm. In running clear across the smear, one might come upon a single polynuclear, or two or three at most; but at the very end of the smear, in a dense windrow, one might find a mass of cells many of which had the appearance of being degenerated polynuclears. Their structure, to be sure, was ill defined; their seemingly nuclei were jumbled and as it were compacted; and they were crowded together in such fashion that no trace of distinct cytoplasm remained. These cells took the stain faintly, like the large monocytes already referred to; yet they showed traces of nuclear structure not to be seen in the large monocyte, and one felt that they were of a different type. These cells did not appear in the earlier smears; and I am led to question whether perhaps their presence suggests a tendency to restocking of the blood with the hitherto minimized neutrophiles.

It is further notable that in the most recent smear I detected a single gigantic eosinophile, with three discrete nuclei, the cytoplasm abundant and sharply defined, and taking a brick-red color, the individual granules very small. In this most recent smear, also, there appeared to be larger numbers of large monocytes that show a fairly distinct nucleus differentiated from the cytoplasm. The total number of the large monocytes, as contrasted with the lymphocytes, has also conspicuously increased. In a single field of the microscope, for example, using the 1.9 millimeter objective and Number 10 eyepiece, and further minimizing the field by lengthening the tube, the count showed fifteen small lymphocytes and twenty-one large monocytes, with not far from one hundred red corpuscles. Another field showed only eight small lymphocytes and twenty-three large monocytes. Such a preponderance, however, was unusual; and fields could be found where the relative numbers were reversed. Thirty fields in succession revealed only a single polynuclear.

The total leucocyte count at this time is 1,048,000, as against a red-cell count of 2,324,000. Yet it is an astonishing fact that this patient, aside from the still noticeable enlargements at the sides of the neck (which, however, are no longer extremely conspicuous), might readily pass under fairly close inspection as a

man with the appearance of robust health. His skin has a good healthy glow, his actions are vigorous and energetic; and he reports himself as feeling exceedingly well. His appetite is so good that he has to curb it to prevent overeating; he sleeps well (although obliged to get up several times to empty the bladder,—the urine, however, showing no abnormality on analysis); and he is able to perform fairly vigorous labor, such as wood-sawing, shoveling snow, and the like, and in general to execute the duties incident to keeping his modest country establishment in order, without experiencing shortness of breath or undue fatigue. His pulse, during his visits at my office, has ranged from 72 to 80; and the blood pressure from 145 to 130,—a fairly characteristic reduction under Proteal treatment. In a word, the clinical symptom-complex is that of a man substantially normal, well preserved, and more than moderately active and robust for his age.

All this, it will be observed, with a total corpuscular count of about three and a third millions, of which leucocytes comprised more than a million; leaving (according to the most recent count) only 2,324,000 erythrocytes; and providing a hæmoglobin index of 70.

Incidentally, I may suggest that the fact that this patient appears not to suffer in the least from lack of oxygenation of the tissues gives strong support to the Proteomorphic thesis that the full normal equipment of red corpuscles is by no means necessary for the carrying of oxygen; for of course it is not to be supposed that the leucocytes can compensate the red corpuscles in this regard; moreover, even if they were able to do so (no such suggestion is made), the total number of corpuscles is still not much above three-fifths of the normal. However, cases of other types are common enough in which an erythrocytic equipment of 3,000,000 or even 2,000,000, suffices to oxygenate the tissues.

The anomaly is, that the universal processes of food hydrolysis and of bodily metabolism in general in this case have been carried out for a term of years with a corpuscular equipment so strangely maladjusted.

But the mystery is to some extent clarified if we accept the general thesis of the Proteomorphic theory and the special interpretation of that thesis just elaborated, according to which the functions of the different types of leucocytes overlap or are complementary, permitting what might be described as team work, through which weakness in one leucocytic department may be effectively compensated in another; and that similar team work is possible between the white corpuscles and the red, as regards the proteolytic functions of the latter.

These theoretical assumptions, considered in the light of such a case of lymphatic leukæmia as that just recorded, give us at least

suggestive clues as to the origin of this obscure disorder. A tenable hypothesis would appear to be that degenerative changes had taken place in the particular cells of the bone marrow that normally produce polynuclear leucocytes; involving also, to a less extent, associated mother-cells of the erythrocytes. To meet this deficiency, unusual cohorts of small lymphocytes were called into action; and as the need persisted, and was perhaps progressively aggravated with progressive degeneration of the cytogenic apparatus in the bone marrow, there was hyperplasia of the entire lymphatic system (roughly analogous to the compensatory hypertrophy of heart muscles to maintain an obstructed circulation), of which tangible evidence was given in the observable enlargement of the lymphatic glands in many regions.

Observation of the smear before Proteal treatment was administered, taken in connection with the clinical symptoms, appears to justify the inference that small lymphocytes in superabundance may on occasion perform the totality of leucocytic labors plus a certain amount of the work of the red cells, maintaining a fair semblance of normal bodily metabolism.

It would appear that the Proteals stimulated the mother-cells of the large monocytes effectively, and that these cells were able to take the work off the small lymphocytes to such an extent that the enlarged lymphatic glands could be reduced; such reduction being perhaps facilitated by direct activities of the large monocytes, as has been repeatedly observed in cases showing malignant metastatic involvement of the lymphatics.

The appearance of increased numbers of polynuclears, albeit in an embryonic or degenerative condition, suggests that possibly the Proteals have been able to stimulate to some extent the exhausted mother-cells of this type of leucocytes. Such stimulation has apparently not been very effective hitherto, however, and the stimulus to the mother-cells of the erythrocytes has seemingly been even less effective, since the number of these cells, although fluctuating (at one time reaching 3,400,000), has on the whole failed to increase. It should be remarked, however, that the possibilities of Proteal stimulation in this direction have been by no means exhausted; inasmuch as the dose administered has not been increased above eight minims. The treatment has been carried out under somewhat disadvantageous circumstances, the patient coming to my office only occasionally, and in the main depending upon home administration. Moreover, it has been thought well to advance cautiously in view of the extraordinary blood conditions to be dealt with.

Fuller history of the case awaits later presentation; I have dwelt on it here because of the interesting sidelights that it throws on the Proteomorphic theory, and because of the conspicuous

clinical betterment that attended the use of the Proteals in a case well calculated to puzzle the therapeutist. All questions of blood picture aside, the progress of the case, as viewed from the patient's standpoint, has been exceedingly gratifying. Parotid glands that constituted a conspicuous deformity have been reduced to less than half the original size, ceasing to be very unpleasantly noticeable; lymphatic nodules larger than hickory nuts have been reduced to the vanishing point; persistent pain in connection with these enlargements has totally disappeared, without recurrence up to the present, and the patient's general health, though never greatly impaired, has been raised to a higher level of seeming vitality, while the sense of well-being has naturally increased with the vanishing of pain.

Studying the Blood Smear

I have a few additional suggestions to make as to compensatory relations of the different types of leucocytes *versus* the army of erythrocytes; but before going on to these, I would like to call attention to certain practicalities of the study of the blood smear that are highly essential if one is to gain a really accurate knowledge of the actual conditions which the smear is capable of revealing. This section can have no great interest for any one who does not work with the microscope, but I believe it will be found to have genuine importance by a good many observers who regard themselves as accomplished students of microscopical blood conditions. Experience has taught me that some very elementary considerations in the study of the smear are often overlooked, and that skilful hematologists may employ methods of making the differential count that necessarily vitiate or invalidate their results.

It is a not uncommon error, for example, as a good many smears sent me for examination show, to use too large a drop of blood, so that the smear runs off the end of the slide. Differential results are entirely vitiated in such a case, if, as often happens, the white corpuscles have an agglutinative quality and thus tend to clump at the end of the smear—since, in this case, the end of the smear will be altogether lacking. It is impossible, in such a case, to gain more than a vague notion of the true character of the differential count from the most careful examination of the smear. The data for an accurate accounting are absolutely lacking.

Assuming, however, that the smear is properly made, the entire content of the drop placed on the slide being available for observation, it is still possible to examine it in such a way as to draw entirely unwarranted conclusions as to the differential leu-

cocytic relations. I have known an observer, for example, to make the count by running up and down the field, thus taking in cross sections, instead of working backward and forward laterally along the entire length of the smear. A moment's consideration makes it clear that if the leucocytes are not evenly spread on the smear, such a method may give a record that quite negatives the facts.

It is true that strictly normal blood may show a fairly even distribution of the different types of leucocytes at different stages of the smear. But the distribution is probably never absolutely uniform, and with the blood of a patient suffering from a protein toxæmia of any type there is likely to be the most striking unevenness. Not infrequently the small lymphocytes are nearly all left near the beginning of the smear, whereas the polynuclears and large lymphocytes, and in particular the large monocytes, are dragged along toward the end of the smear. In such a case the result of a cross-section examination (up and down the field as the examiner views it, instead of from side to side), will depend very largely upon the particular point that chances to be brought under observation. If the survey is made near the beginning of the smear, the report will show a tremendous preponderance of small lymphocytes, if, on the other hand, it is made near the end of the smear, there will be a corresponding preponderance of polynuclears or large monocytes. In either case, the accounting is worse than worthless; it conveys an entirely wrong impression of the facts.

But the difficulties of such a case are not entirely solved merely by making the lateral survey. It is true that such a survey will put one on the trail of the different types of leucocytes and will ultimately bring all types into the field, whether they have stopped at the beginning of the smear or have been carried to its extremity—provided, of course, that the entire length of the smear is examined. But a point I have never seen emphasized is that, quite obviously—when your attention is called to it—you do not get an accurate record if you discontinue counting while in the midst of the smear. It is perfectly clear that such is the case, if you are going once across the smear only, since in that case you may not have come to the portion of the smear that contains the chief bulk, of, let us say, the large monocytes. But a moment's reflection will make it clear that if, after going across the smear, you turn about, in the regular way, and proceed in the reverse direction, you must now go clear back to the beginning of the smear, else you will not give proper enrollment to the small lymphocytes that were largely left near the bginning.

However often you repeat the process, you must never stop short of a complete traversing of the smear, if you are to give

proper enrollment to the differently distributed types of leucocytes.

Yet I venture to surmise that nine observers out of ten disregard this truism, and ultimately stop their count when they have registered an arbitrary number of corpuscles, say two hundred or three hundred, regardless of the fact that the field with which they abandon the count may lie at the middle of the smear.

If the smear is a short one, so that a good many tours have been required to make up the requisite count of two hundred or three hundred, the miscalculation will not be very notable, but if a long smear is under observation, or if there is a marked leucocytosis, so that only two or three sweeps of the smear are necessary to complete the count, the inaccuracy may be highly significant. Smears are not infrequent, for example, in which practically all small lymphocytes are in the first half and practically all the large monocytes in the second half. If, now, the sweep of the field begins at the beginning of the smear, and two and a half tours of the field are required, the region of the small lymphocytes will have been traversed three times, whereas that of the large monocytes will have been traversed only twice, and the record will show a seeming preponderance of small lymphocytes in excess of the actuality—somewhat in the ratio of three to two. But if, contrariwise, three and a half tours of the field were required, then we shall have traversed the region of the large monocytes four times and the regions of the small lymphocytes only three times, and the record will show a fictitious preponderance of large monocytes.

In a word, where the method is employed—and it is almost universal—of counting a definite number of leucocytes, it can occur only in the exceptional instances where the count happens to be finished at the extremity of the field, that the result is as accurate as it might be and should be. The degree of error will vary with the length of the smear (a short smear being preferable) and with the aggregate number counted; the larger the number, naturally, the closer approximation to accuracy. But the method is inherently faulty and, in my opinion, should be abandoned.

The only correct way to make the differential count, as I see it, is to work clear across the field from right to left and from left to right, several times, preferable at considerable longitudinal intervals, so that in the end practically the entire area of the smear has been sectioned, and to stop counting, not when an arbitrary number has been reached, but at the end of a complete tour across the smear, whether that tour be the first or the twentieth. A single or double sweep across the field, with an aggregate count of, let us say 137 leucocytes, would be, in

my opinion, more accurate in its results, particularly where a long smear is in question, than an arbitrary count of 200 or even of 300 cells; although, of course, it is not open to dispute that, other things being equal, the larger the count the closer the approximation to accuracy. Other things are not equal in the supposititious cases in question.

The method of counting an arbitrary even number of cells has nothing whatever to recommend it except ease in computing percentages. Every other advantage lies with the method of counting clear across the field, letting the aggregate number be what it may (but continuing, of course, until the aggregate is reasonably large), and the additional labor of computing percentages with this method should not weigh for a moment against the enhanced value of the results.

Intestinal Toxæmias and the Corpuscular Balance

Turning now from this parenthetical excursion into the region of microscopic technique, which I trust was not altogether unwarranted, let us make further examination of the corpuscular balance, with particular reference to the response to protein invasions from the intestinal tract. Let me say at once that the observations of the blood falling within this classification are likely to be very discordant. We have considered cases in which intestinal toxæmia was associated with very pronounced leucocytosis. There are other cases in which there is a pronounced leucopœnia. Sometimes, at least, the conflicting evidence may be reconciled by considering the degree of chronicity of the cases involved; recalling that habitual stimulation of the cytogenic apparatus throughout a long period may lead to exhaustion. I have records of several cases of rheumatoid arthritis, of many years' standing, in which the outstanding feature of the blood count is a conspicuous paucity of leucocytes. Usually with these cases there is a history of life-long tendency to constipation, associated with habitual over-indulgence in proteid foods.

Presumably, in these cases at an early stage, there was overstimulation of production of leucocytes to meet the protein invasion. Exhaustion has followed, and the leucocytes, performing their functions inadequately, have put an excessive burden on the red corpuscles. In general the erythrocytes have appeared able to meet in some measure the recurring emergency, as shown by their relatively large numbers, but the inadequacy of their ultimate action is evidenced in the incomplete metamorphosis and elimination of protein end products, in particular uric acid. The weak spot in the heredity armor of the individual being the fibrous tissues and serous membranes of the joints, deposits of

urates occur here, with the gradual development of the characteristic malformations of chronic arthritis.

There is nothing in these end-product deposits to give new stimulus to the mother-cells of the leucocyte. The case is different, however, with an individual, who, with the same ætiological conditions, as to protein invasion, has an hereditary predisposition to hyperplasia of cells under stimulus of a local irritation which may lead to the development of a malignant neoplasm.

I have elsewhere developed the thesis (see the *Monograph*) that the essential characteristic of malignancy in a neoplasm is that its cells are more or less subject to proteolysis by the corpuscular enzymes. According to this view, the cancer cells, in thus undergoing hydrolysis, stimulate the blood-forming mechanisms and lead thus to leucocytosis, and in particular to large monocytosis. Whether the sequel will show complete hydrolysis and elimination of the cancer cells or not depends upon the persistence of the local irritative stimulus, the degree of development of the cancer cells themselves, the responsiveness of the blood-forming mechanism, and other factors that do not here concern us. What is here significant is that one does, in point of fact, find a leucocytosis, and a relative monocytosis, as the almost constant accompaniment of a cancerous invasion; and that the stimulus given by the disintegrating cancer cells themselves may be supposed adequately to explain the condition, in contrast with the leucopœnia of the arthritic patient who lacks this stimulus. But I repeat that, could we have seen the arthritic patient at an earlier stage, we should probably have found that the protein invasion (usually from the intestines) had produced a leucocytosis that long persisted before exhaustion of the cytogenic mechanism came about. In substantiation of this view, we not infrequently find a leucocytosis, and in particular a notable large monocytosis, present in young individuals suffering from intestinal toxæmia, in whom the cytogenic apparatus is still responsive. Moreover, such an increase has been observed in cases of intestinal toxæmia that have not undergone proteal treatment; although in other cases of this type (as above noted) the large monocyte count is low.

Here, for example, is a man of 26, who has suffered all his life from intestinal toxæmia. So poor is his assimilation that, even when in best condition, he is almost skeletal, carrying no excess avoirdupois whatever. His stomach is his perpetual enemy. His differential count shows 50 per cent. polynuclears, 34.3 per cent. small lymphocytes, 22 per cent. large mononuclears, and 0.6 per cent. eosinophiles. It is observed that the small lymphocytes are mostly relatively large and with abundant cytoplasm, so that one is constantly tempted to classify them as large

lymphocytes; yet even so the number of cells registered as unequivocal small lymphocytes is at a high normal limit. Meantime the large mononuclears, which are seen to stain deeply and with ill-defined nuclear bounds, represent 22 per cent. of the leucocyte count, a proportion seldom observed except under the stimulus of proteantigen treatment. The nuclei of all the white cells stain very poorly, a second staining with methylene blue being required to bring them out at all clearly.

An explanation of these peculiarities, consonant with the hypothesis all along expounded, would be that in this case stomachic and intestinal digestion are so defective that relatively large numbers of unbroken protein molecules find their way through the intestinal walls. This invasion is met by a large mononuclear population, and in particular by the extraordinary aggregation of large monocytes. The condition here is strictly comparable to the conditions that obtain where there is a well-developed cancer; in each case there is constant intrusion of fully formed proteins into the circulation, and the increase in large monocytes shows the response of the defensive mechanism. The relative effectiveness of response in this case may be explained, perhaps, by the fact that the patient is young and hence has a more resilient cytogenic apparatus than the average cancer subject.

The particular case of intestinal toxæmia in question is known to me only by report and from a blood smear sent to me from a distance, so I am not able to record the results of Proteal treatment, which would be of obvious interest. I have had numerous cases of intestinal toxæmia more or less similar to this, however, under treatment, and I am able to report that the results of Proteal treatment have in most instances been as satisfactory as the theoretical consideration above outlined might lead one to anticipate. As a rule, these cases do not have a high large monocyte count at the outset, presumably because their digestive protein products are at an intermediate stage of decompounding before they penetrate the intestinal walls. The red cells, however, whether or not they are reduced in number, are likely to show very marked abnormalities of form, suggestive of perverted function; and the white cells, frequently increased in number, tend to take the stain very badly, and to have an agglutinative quality that leads to their clumping and assembling in windrows at the end of the smear. Very commonly the red cells in the Toisson solution show a large proportion of small or misshapen cells, battered looking, crenated, or covered with spicular pseudopodia, giving them an appearance that I am accustomed to liken to that of a miniature sea urchin. There may be

curious vacuolations or typical modifications of the structure giving a figured appearance.

All these things, to be sure, may be seen more or less in relatively normal blood cells; but the proportion of cells showing such aberrant conditions is very greatly increased in cases of intestinal toxæmia, particularly when associated with rheumatic sequels. One cannot well doubt that there are profound chemical changes in both red and white cells of such a subject.

A typical case recently under treatment is that of a young woman whose clinical symptoms included "general debility," poor circulation associated with cold hands and feet, lack of appetite, lassitude and depression, and a tendency to enlargement and pain of the finger joints of "rheumatic" character.

The blood count showed 3,571,000 red corpuscles of characteristic abnormal quality, and 9,690 white cells of the faint-staining, clumping variety. The polynuclears represented 82.6 per cent., small lymphocytes 9.6 per cent., the large mononuclear 7 per cent., and the eosinophiles 0.6 per cent.

After three weeks of Proteal treatment (Nos. 37 and 45 in doses of 3 to 6 minims on alternate days), there was marked improvement all along the line in clinical symptoms, including conspicuous change in the patient's appearance and feelings, and the blood count showed more than 6,000,000 red cells which at first seemed normal, but afterward became picturesquely modified along the lines just referred to. The white cells had been reduced to 5,800, and there was most striking modification of the differential count, which now showed 59.5 per cent. polynuclears, 26.5 per cent. small lymphocytes, and 14 per cent. large mononuclears. Occasional normoblasts and groups of platelets were now present. A modification of the chemical condition of the whites was suggested in the fact that the nuclei now stained deep purple, the cytoplasm being markedly acidophile. The individual leucocytes were large, and there was not much clumping.

This patient, obviously, requires a long course of proteal treatment to bring about permanent modification of the disturbances of metabolism, but the changes effected in so short a period are striking and gratifying. The case is still under treatment.

By Way of Summary

The reader of the Monograph on *The Proteal Treatment of Cancer* is aware that the theory that underlies my interpretation of most of the phenomena of protein therapy traces a large part of the ills of middle life to disturbances of protein metabolism.

It will be recalled that I listed lymphatic and myologenous leukæmias and pernicious anæmia, and such seemingly diverse conditions as anæmic obesity, Graves' disease, arthritis, arteriosclerosis, and neoplasms of all types under a common heading as evidence of the "cancerous condition." The detailed exposition of a certain number of typical cases in recent pages has been intended to illustrate in some measure the validity of this classification. In my original exposition of the principles of protein therapy, so often referred to in these pages, I spoke of the proteantigen response as applicable to all types of protein infection. The present entire volume is but an elaboration of that thesis.

It is perhaps unnecessary to detail further individual cases to emphasize the opinion that disturbances of the blood growing out of abnormal alimentation may be ætiologically connected with many types of maladies that have not hitherto been associated in the mind of the average practitioner. It should be axiomatic to say, however, that abnormal modifications of the blood must have wide and various implications in disturbed functionings of the bodily organs. It is scarcely too much to say that there are no maladies that are not to some extent associated with disturbances of metabolism that must register themselves in the blood, whether or not we are able to read the record.

Every practical physician knows how prevalent are anæmias of various types, whether or not associated with recognized sources of protein infection. But the manner of association—the universality of disturbed protein metabolism as a factor in producing anæmias—was perhaps never so adequately explicable on any other hypothesis as it becomes when interpreted in the light of the Proteomorphic theory. And assuredly there is no remedial agent hitherto available that so directly and so explicitly goes to the source of disturbance and tends to correct it as do the proteantigens.

It will be a little difficult for the profession to accustom itself to the idea that the same line of treatment, modified to meet individual cases, may be applicable to maladies recorded under such diverse headings as intestinal toxæmias, anæmias, arthritis, psoriasis, asthma, tuberculosis, and cancer. But when the idea is clearly grasped that there are important underlying causal factors that are the same for all these conditions, the logicality of the protein treatment will be obvious.

And I predict with much confidence that the practical physician, whatever his attitude toward theories of therapeutic action, will feel that Proteal medication places in his hands a new weapon of unique value in the treatment of a wide range of maladies of middle life and old age that hitherto have proved

intractable. When he has seen the blood count in an anæmic patient change more radically after a week or ten days of treatment than he would otherwise have been able to change it in as many months, he will come to recognize the Proteals as indispensable additions to his equipment, compared with which the entire list of specific serums and vaccines have minor significance.

In speaking thus, I have no intention to disparage the value of specific serums and vaccines. I have been from the outset an enthusiastic advocate of these methods. I have only in mind the thought that the diseases to which they are applicable are relatively rare; whereas the maladies herein under consideration, as associated with disturbed protein metabolism and more or less amenable to Proteal medication, are so prevalent that they claim by death three-quarters of a million individuals in the United States each year. I think it is not quixotic to express the belief that a more intelligent application of dietetics combined with the rational use of Proteal therapy may modify very conspicuously the mortality statistics of the not-distant future.

I bring this outline of the development and present status of protein therapy to a close with a full sense of the inadequacy of the presentation that has been given. I have not so much as referred to the recent literature that shows how actively the minds of many physicians in various parts of the world are turning toward the subject. My intention throughout has been to give a résumé of the pioneer work in this field; my own experience and the experience of co-operating physicians still constituting, no doubt, by far the largest body of evidence in existence as to the therapeutic use of non-specific proteantigens. It suffices to say that the reports that have come from a number of independent workers in this country and in Europe during recent months, although covering only a part of the field of our researches, have been singularly corroborative of our results. In particular, the work of Müller and Thanner and their associates in Berlin in the use of milk protein and an "albumose preparation" in the treatment of infective maladies of the eye, including those of syphilitic, of rheumatic, and of gonorrheal origin, have peculiar interest. Such extensions of the method will excite no surprise in any one who has grasped the principles of the therapeutic action of the proteantigens, as originally detailed in my paper of October 2, 1915, and as elaborated throughout this book. Disturbed protein metabolism underlies a great variety of maladies, particularly in middle life and old age; and, as my original presentation stated, protein therapy is directed "against all protein infections."

Even where the infection is specifically bacterial there is

theoretical warrant for the administration of agents that stimulate the blood-forming mechanism to effective activity, since "good blood" is always at a premium. Moreover, it is plausible to suppose that when the cytogenic apparatus is thus rendered active, its functionings will result, under proper stimulus, in a maximum production of specific anti-bodies directed against the toxins of a particular bacterium, as well as of general enzymes to deal with the proteid bodies of the bacteria themselves.

It appears fairly certain, then, that the range of application of non-specific protein therapy overlaps the field of specific therapy, and has even wider connotations than those included in the practical use of the method up to the present. Yet even as the case stands at the moment, protein therapy, of proved value in conditions ranging from anæmia and intestinal toxæmia to typhoid fever and tuberculosis, and from rheumatism to cancer—a method, in short, that combats every form of protein toxæmia by fortifying the bodily defensive and offensive mechanism as represented in blood-forming organs and blood corpuscles—may without exaggeration be said to constitute the most general and the most comprehensive procedure known to modern scientific therapeutics.

It is my confident belief that in the very near future non-specific protein therapy—and in particular Proteal therapy—will be so generally employed as to modify the mortality statistics of the degenerative diseases of middle life and old age not less conspicuously than the mortality of diphtheria has been modified by specific serum therapy and the mortality of typhoid fever by the anti-typhoid vaccine. In its ultimate application, Proteal therapy will find a prominent place among preventive measures and in the incipiency of disorders of nutrition. In its earliest application to the later stages of the most malignant of disorders of disturbed metabolism, it showed astonishing efficacy; but the full measure of its value can be taken only when it is generally used to counteract disorders of nutrition in their incipiency—simple anæmias, neurasthenias, mild autointoxications, "run-down" conditions—or at a stage short of profound cachexia and permanently degenerated organs. The present book will have served its purpose if it arouses the profession to a realization of the enheartening possibilties along these lines now made available by protein therapy in its wider aspects.

PART II

CANCER: INTERPRETED IN THE LIGHT OF THE PROTEOMORPHIC THEORY AND THE PROTEIN RESPONSE

The ensuing pages reproduce with occasional modifications about two-thirds of the text of the Monograph so frequently referred to in this book, as published December 1, 1916, under title of *The Proteal Treatment of Cancer and Allied Conditions: A Practical Study of a New Therapeutic Principle as Interpreted in the Light of the Proteomorphic Theory.*

I have thought that it might be of historical interest to include the dedication of that work, which is therefore reproduced overleaf.

This monograph

telling of a humanitarian work that vitally concerns the lives and welfare of one-sixteenth of the world's total population,—a work carried forward in the face of fanatical opposition, under almost insuperable difficulties, and at great personal sacrifice,—

is dedicated

to the memory of five of my New England ancestors—representing four patronymic generations in direct line—who were Regular physicians of distinction, namely:

(1) My great great grandfather, THOMAS WILLIAMS, A.M. (Yale), M.D. (1718-1775), Colonial surgeon in the French and Indian wars and brother of the founder of Williams College; my great grandfathers (2) WILLIAM STODDARD WILLIAMS, M.D. (1762-1828), of Deerfield, Mass., and (3) JOSEPH GOODHUE, M.D., of Portsmouth, surgeon in the Federal Army; (4) my grandfather, STEPHEN WEST WILLIAMS, A.M., M.D. (1790-1856), Professor and Lecturer upon Medical Jurisprudence, the Theory of Medicine, and Medical Botany, in the Berkshire Medical Institute, in the College of Physicians and Surgeons in New York, in Dartmouth College, and in Willoughby University; author of numerous books; personal friend of Valentine Mott and Oliver Wendell Holmes; close associate of N. S. Davis in the organization of The American Medical Association; and (5) EDWARD JENNER WILLIAMS, M.D. (1823-1881), my father, a man endowed with rare qualities of mind matched by yet rarer qualities of heart:

Each of them perennially active in the service of humanity; each of them in the forefront of the medical progress of his time; each of them a life-long zealot for the best traditions of medical ethics; each of them honored by all who knew him in life, and in death epitaphed simply and justly with the words:

"He was a skillful practitioner and an honest man."

PART II

CANCER: INTERPRETED IN THE LIGHT OF THE PROTEOMORPHIC THEORY AND THE PROTEIN RESPONSE

SECTION I

THE NATURE OF CANCER

In the paper of October 2, 1915, in the *New York Medical Journal,* I suggested the following definition and interpretation of cancer:

One might define cancer, in the light of the present theory, as a systemic condition characterized by the development of neoplastic cells of a somewhat embryonic type, in conjunction with an excess of leucocytes in the blood and a deficiency [actual or relative] of red blood corpuscles.

It must further be postulated that the neoplastic cells are of a type susceptible to the attacks of leucocytic enzymes, so that there is a constant tendency to disintegration of some of these cells under the attacks of the white blood corpuscles. Meanwhile, the deficiency [actual or relative] in red blood corpuscles makes it impossible for the system to deal adequately with the partially hydrolyzed protein products resulting from the breaking down of some of the new cells under the attacks of the leucocytes. The net result is a condition of protein poisoning or autointoxication which, when fully developed, constitutes the characteristic "cancer cachexia," and ultimately causes the death of the patient.

It should be observed that this new definition of cancer explains the hitherto obscure fact that almost any kind of new growth in the organism may on occasion take on the characteristics of malignancy. A fibroid tumor of the uterus, for example, is not ordinarily "malignant" because its tissues are of a type that the leucocytic enzymes cannot readily attack—largely, perhaps, because of their slow development and firmness of texture. Yet on occasion, as is well known, portions of a fibrous growth may become susceptible to disintegration under the attacks of the bodily enzymes; and in such a case, should the red blood corpuscles fail of their appointed task, a condition of veritable malignancy is attained, and the aforetime fibroid becomes a cancer.

Ordinarily, however, the neoplastic growth is from the outset composed of such cells as are more or less susceptible to the

action of the leucocytes; and, from a pathological standpoint, it is permissible to regard all such growths as nascent cancers. In a vast majority of cases, however, the neoplasm is denied opportunity of considerable growth, because of the immediate attacks of the leucocytes, which are backed up by the erythrocytes to such good effect that the neoplastic proteins are completely dissociated and eliminated from the body without producing harmful results, and, indeed, as a rule, without being given any consideration whatever.

It is probable that there are scores of nascent neoplasms that are dissociated and obliterated for every one that attains mastery over the corpuscular bodily defenders and becomes a tangible neoplasm. It is probable, in other words, that every insignificant lesion of the bodily tissues that calls for the development of new cells in the process of repair, might be regarded as an incipient malignant neoplasm; and is prevented from becoming an actual menace only by the efficient activities of the corpuscles that are normally present in adequate numbers for the bodily defense.

In elaboration of the idea underlying this conception of cancer, I now suggest the following expanded definition:

Hyperproteomorphism, or the Cancerous Condition, is a systemic condition characterized by a profound disturbance of protein metabolism involving originally the blood and blood-forming mechanism; evidenced by disturbances of the corpuscular balance and the abnormal proliferation of cells of one type or another; frequently, *but not necessarily*, associated sequentially with local neoplasms comprising cells that are partly subject to hydrolysis under influence of the enzymes developed by the white and red corpuscles.

As elaborating the definition, I suggest the following classification of the varied manifestations of the cancerous condition:

(1) Lymphatic and Myelogenous Leukæmias and Pernicious Anæmia, where the hyperplasia involves the blood-forming tissues.

(2) Anæmic obesity, characterized by excessive fat-foundation and deposit, at the expense of more useful tissues.

(3) Proteoid hypertrophy, as in Grave's Disease and myxoedema, where the lawless new growth involves glandular and lymphatic tissues.

(4) Chronic rheumatoid arthritis, where the maladjustment of metabolism manifests itself in a tendency to new growths in connection with the cartilage of the joints.

(5) Arterio-sclerosis, where the localized evidence of nutritional maladjustment involves the tissues of the circulatory apparatus.

(6) Benign neoplasms, where a local irritation in association with the disturbance of protein metabolism has led to a prolifer-

ation of localized tissues not freely subject to proteolysis by the corpuscular enzymes.

(7) Malignant neoplasms, or true cancer, where a localized irritation or abrasion has cooperated with protein maladjustments to cause a proliferation of epithelial, endothelial, or connective tissues constituting a more or less conspicuous neoplasm the tissues of which are to some extent subject to hydrolysis by the corpuscular enzymes. Here the development of the neoplasm in itself evidences the disturbed conditions of protein metabolism in the body (deficiency of corpuscular enzymes), and the new cells tend further to disturb that maladjustment by presenting additional protein material for hydrolysis.

I am fully cognizant that so revolutionary a definition and classification as the above, in which it is suggested that the cancerous condition is not necessarily associated with the presence of such a neoplasm as is commonly supposed to constitute the essentials of the disease, must excite surprise and opposition. But I venture to believe that the more closely the matter is considered, the more valid will seem the reasoning on which the interpretation is based. It will appear presently that there is also an important body of clinical evidence that gives support to the view above presented.

SECTION II

THE ORIGIN OF CANCER

What I have to suggest as to the origin of cancer follows as a matter of course from the theory just outlined as to the nature of the disease.

Whatever tends to disturb protein metabolism in the body may be considered as a predisposing cause of the malady. Familiar causes of such disturbance are (1) lack of exercise, (2) excess of protein food, particularly of animal proteins, (3) inadequacy of the protein intake.

It is obvious that the second and third of these causes of protein maladjustments are mutually exclusive. They must both be borne in mind. An excess of proteins in the diet, resulting in a putrefactive mass in the bowels and the entrance of a certain amount of unbroken protein into the parenteral system may overwhelm the blood corpuscles and produce an anæmic condition comparable to that due to a lack of adequate protein for the building up of fresh supplies of blood corpuscles.

It will be recalled, of course, that there is constant destruction of the red corpuscles in the spleen and liver, through which

(according to the proteomorphic theory) byproducts of protein metabolism that are toxic in character are excluded from the system. To compensate this destruction, there must be a constant building of new corpuscles, implying fresh protein supplies and an enormous aggregate expenditure of energy. If the necessary protein supplies are brought in excessive quantities, it follows that the red corpuscles have an excess of byproducts (of the polypeptid order) to deal with and are necessarily destroyed in excessive numbers. To keep up the supply, calls for an increased expenditure of energy, putting a needless tax on the bodily machine that may manifest itself in an abnormal blood count, increased blood pressure, and ultimately in one or another of the conditions of localized maladjustment above listed.

But it does not by any manner of means follow that the only cause that can produce such maladjustments is an excess of protein in the digestive tracts. It has already been implied that a marked deficiency might lead to a corresponding sequence of events. The presence of large numbers of bacteria in the intestinal tract is in itself a factor that makes constant work for the red blood corpuscles, resulting in a steady nitrogen loss and necessitating a constant restocking with nutritive proteins. So protein starvation might be quite as disastrous as protein repletion. The happy mean, here as elsewhere, constitutes the road to health.

As to exercise, a somewhat similar line of reasoning applies. Every physician nowadays recognizes the necessity for a certain amount of exercise in normalizing the processes of metabolism. But it must not be overlooked that excessive exercise, carried to the point of exhaustion, may have a devitalizing influence that will lead to conditions closely comparable to those resulting from entire lack of exercise. Doubtless a hundred persons suffer from lack of exercise, however, where one suffers from over exercise. So the practical lesson that one is commonly called upon to inculcate is that exercise is the road to health.

Vigorous exercise is a recognized factor stimulating formation of blood corpuscles; which fact, according to the present theories, suggests a fairly direct association between exercise and prevention of the disturbances of protein metabolism that are here postulated as constituting the true cancerous condition.

Whereas lack of exercise and improper diet are, in my opinion, the chief causes that lead to the maladjustments of metabolism constituting the cancerous condition, there are, as a matter of course, many minor causes of disturbance. Conspicuous among these is the loss of blood which many women suffer at the menopause; a condition that no doubt contributes very markedly to the genesis of malignant neoplasms; a condition, therefore, which

should always receive careful attention from the physician. Any condition that causes persistent anæmia should be viewed with solicitude in this connection.

A greater or less degree of instability conditioned on heredity, is implied as a matter of course, as determining a "tendency" to cancer. Hormone disturbance (e. g., thyroid inefficiency) may also constitute a predisposing element.

As to causes that determine the localized development of a neoplasm, when the cancerous condition eventuates in such development, elaborate studies have been made, and there is virtual unanimity of opinion among authorities. Any chronic source of irritation may result—and indeed must result—in stimulus to growth of new cells. A callous on the thumb and a corn on the toe illustrate this principle as tangibly as an epithelioma on the lip where a clay pipe has long been held, or a carcinoma of the breast that developed from a nipple irritated by a corset steel. But the thumb callous and the corn are "benignant" growths because their tissues are not of a character to be broken down by the bodily enzymes. The same is true of an ordinary overgrowth of fibrous tissue in the interior of the body, as a fibroid of the uterus or a fibroma located, for example, on the forearm.

The new growth, let it be emphasized, becomes malignant only when its character is such that its cells can to some extent be hydrolyzed by the bodily enzymes (including, prominently, according to present thesis, the enzymes of the white and red corpuscles). Moreover, even cells falling within this definition are not necessarily a menace to the system, provided the supply of enzyme-forming corpuscles is adequate and in good working order; for in that case misplaced new cells are at once dissociated and the products of such dissociation utilized as animo-acids or eliminated from the body. According to the proteomorphic theory, the early stages of such dissociation are effected by the white corpuscles, and the later (polypeptid) stages by the red corpuscles; but details as to this are not essential to the present thesis. What is essential is the recognition that if the enzymes that are competent to hydrolyze cells, whenever these cells are present in excess, are normally abundant in the system, there will be no development of a malignant neoplasm.

Stated otherwise, the presence of the tangible "malignant" neoplasm is in itself evidence that there was antecedent disturbance of the processes of protein metabolism in the body, characterized specifically by inadequacy of the enzymes that deal with proteins not needed by the system.

Viewed from a slightly different angle, it appears that any proliferation of new cells, however induced e.g., in repair of an

ordinary traumatism—is a potential malignant neoplasm; the question as to whether it becomes an actual menace being determined solely by the antecedent conditions of bodily metabolism. As illustrating the truth of this, it is familiarly known that normal blood antagonizes cancer cells when introduced from without, as in the case of an inoculation experiment in animals. It is known, too, that transplantation experiments are facilitated by bleeding the animal in advance of transplantation.

Summarizing the matter, we may say that three factors are always present and in cooperation when a malignant neoplasm develops in the human subject. There is (1) the factor of disturbed protein metabolism, which I have spoken of as the cancerous conditions; there is (2) the factor of local irritation,—a pipe stem on the lip, an injury to the breast, hot food in the mouth or stomach, chronic intestinal irritation, a laceration of the cervix uteri; and there is (3) the factor of inherent susceptibility, hereditary or acquired.

It is the old story of stress and resistence. The same irritation being applied in the same place in the case of two individuals, one individual suffers no obvious inconvenience, because his defensive mechanism is in good working order; and the other individual develops a fatal "cancer" because his defensive mechanism is not in effective fighting condition.

This view harmonizes the contentions of those theorists who have on one hand alleged the general origin and on the other, the local origin of cancer. In a sense both theorists are right, inasmuch as there would probably never be a local neoplasm developed in any individual case, unless there was some source of irritation. So there is every reason why careful attention should be paid to sources of local irritation, and to local injuries of every character. But it is sheer folly, while treating these local conditions, to ignore the underlying systemic maladjustments, correction of which (where this is possible) would make the danger from local irritation negligible.

In other words, in the profounder view, the problem of the origin, and therefore the problem of the prevention, of cancer implies attention to the bodily processes of metabolism—digestion, assimilation, nutrition. Mere attention to local conditions partakes of the character of what Thoreau called clipping at the twigs of the tree of evil while the roots remain untouched. The root of the cancerous condition is disturbed protein metabolism, and not mere local irritation.

I shall have occasion to point out rather obvious corollaries of this view in their application to the question of the surgical treatment of cancer, as well as to make what I hope may be considered important deductions as to more effective general treatment of the malady.

SECTION III

THE LOCAL AND SURGICAL TREATMENT OF MALIGNANT NEOPLASMS

We have seen that the development of a local neoplasm implies defective conditions of general blood supply.

Such deficiencies may be accentuated by local perversion of circulation, as, for example, where the capillaries and veins are rendered patulous by the persistent application of heat, as in the use of a clay pipe, or of the abdominal heaters carried by certain natives of the Orient.

In a slightly different way, the presence of an excess of adipose tissue, may interfere with the circulation, and tend to produce a local anæmia even while the general blood supply is fairly adequate.

In a case in which the general conditions of protein metabolism were just at the border line, so to speak, of the cancerous condition,—that is to say, of out-and-out abnormality,—a comparatively slight interference with circulation at some local point may give opportunity for the development of a neoplasm that otherwise would be held in check.

Such a condition is found, for example, in nearly all scar tissue. Every pathologist knows that scar tissue is poorly supplied with blood vessels, and that it tends rather readily to break down under irritation. In other words, it has not a normal degree of resistance. Doubtless this lack of resistance is closely associated with the defective blood supply. If, now, in addition, there is some source of irritation that tends to stimulate the growth of the cells (as all irritation does tend to do), conditions are favorable for the development of a neoplasm, which will be non-malignant or malignant according to the general condition of the blood, or according to the precise character of the new tissue itself.

If the balance of leucocytes is right, and there is an adequate supply of red corpuscles to deal with the later products of protein decompounding, the new tissue will be cared for by the system, and the condition of malignancy cannot develop.

If, on the other hand, the red cells are inadequate either in number or in activity, the development of the new cells will almost of necessity result in a condition of malignancy.

Even when at the outset the red cells are adequate the growth of the new tissue may be so rapid as to supply a larger amount of protein than can be dealt with (particularly if the red cells

are over-burdened by an excess protein diet), and a condition that at first was non-malignant will gradually grade into malignancy.

Such a change from a benign to a malignant condition is a matter of common observation. As an illustration, note how ulcer of the stomach tends to develop into cancer of the stomach. The presence of the ulcer tends in itself to interfere with digestion and assimilation, and thus to superinduce the systemic maladjustment, as regards protein metabolism, which I have all along spoken of as the cancerous condition. In this case, the initial cause of the entire difficulty may have been the ingestion of a morsel of hot food. The local abnormality here precedes the systemic one; but it should be recalled that in such a case, if the person swallowing the hot morsel of food was in normal health, the original stomach lesion was an ulcer of "benign" character, and its ultimate malignancy was sequential to the general condition of protein maladjustment, as in the case of every other malignant neoplasm.

Cancer of the stomach, however, is a case apart, complicated by the fact that the stomach is the channel of intake of foods to nourish the body in general. With malignant neoplasms in general, it is a safe presumption that there are usually deficiencies of local circulation to supplement the defects of the general blood supply. The uterus depleted by hemorrhage is an illustration in point.

It follows that anything which tends to facilitate the circulation of the blood in and about the malignant neoplasm may be of remedial value, provided that the enzymic conditions of the blood have not shrunk to too low a level.

So we find that a local inflammation may sometimes have curative effects at the early stage of development of a malignant neoplasm. The cardinal symptoms of inflammation—pain, redness, and swelling—are associated with an engorgement of the blood vessels, and thus with an increased local capacity to deal with the protein elements. The true explanation of inflammtion has probably never hitherto been available as clearly as the proteomorphic theory reveals it. Hitherto no one has understood just why there should be an accumulation of red blood corpuscles at a source of inflammation. That the process was curative or beneficial for the individuals could be taken for granted, but as to just what the nature of the benefit conferred might be, has hitherto been only inferential. Now that the province of the red corpuscles in dealing with the end-products of protein metabolism is understood, the benefits of the inflammation induced, for example, by bacterial onslaught are clearly explicable. The province of the red blood corpuscle is to cooperate with the white corpuscles by carrying away and further proteolyzing the later products of protein decompounding.

Where the protein in question is new tissue of cancerous character, the process of decompounding and elimination is of course entirely comparable. The leucocytes (in particular, probably, the large mononuclears) begin the process of hydrolysis, and the red corpuscles continue it beyond the polypeptid stage and carry away the toxic by-products.

So we might expect a certain amount of relief, and even in favorable cases an actual curative process, to be engendered by local inflammation, however induced, in the region of a malignant neoplasm at an early stage. Such an expectation is occasionally justified. I have recently had called to my attention at first hand a case in which, seemingly, an accidental streptococcus infection resulted in the disappearance of an epithelioma of the lip quite without treatment; and this observation is by no means unprecedented. Doubtless there are scores of irritative or caustic compounds that have in exceptional instances produced the "cure" of a local epithelioma, or of a carcinomatous ulcer of the breast, through inducing such a local inflammation.

Such cases, however, would obviously be exceptional, and in general it is to be hoped that a local inflammation will prove curative in any case of a well-developed malignant neoplasm only in occasional instances. As an adjunct to general treatment, however, the application of a local irritant may be of value. But at best this treatment must be considered as an adjunct only.

It is my belief that much the same statement may be made with regard to the efficacy of the treatment of the local neoplasm with the knife. I am aware that this view is heretical, but it follows as a natural conclusion from the line of reasoning above outlined.

To be sure, it is current surgical doctrine that if cancer can be removed early enough, and removed in its entirety, the patient is cured.

But in point of fact, if the present thesis as to the nature of cancer is tenable, the surgeon who has removed a malignant neoplasm,—even in its earlier stages, and even though the removal had been as complete as is ever feasible,—far from curing the malady, has not really treated the malady at all. He has removed a local manifestation of the essential systemic abnormality that is the true "malignant condition," but at best the treatment is a tentative dealing with symptoms, and has no reference to the essential disease itself.

It is true that the removal of the local neoplasm takes away a certain amount of tissue that, through partial dissolution, is poisoning the system; and thus may be a valuable aid in the treatment of the amaladjustment in the process of nutrition, which constitutes the essential character of cancer. But to treat the

local condition, and imagine that in so doing one has cured the malady, is hardly less futile than would be the supposition that one has cured a case of syphilis because one has excised a syphilitic wart or healed a chancre or a tertiary ulcer by local cauterization.

The futility of even the most drastic surgical interference is unequivocally illustrated by the history of a case examined and diagnosed by me in which both breasts and the axillary glands had been removed because of the presence of small nodules which were pronounced of doubtful malignancy by a competent microscopist; yet in which the blood six months later recorded 17 per cent. of large mononuclear leucocytes, half of them myelocytes, leucoblasts, and lymphoidocytes; together with red cells showing poikilocytosis and polychromasia, and not infrequent normoblasts, evidencing a condition of myelogenous excitation that—in connection with the history of the case—left one not at all in doubt as to the existence of the cancerous condition. Here surgery had been given the best possible chance, and had obviously failed. The patient died, untreated, six months later.

It does not follow that the surgeon's knife should be held in abeyance. On the contrary, there is the most logical reason for using the knife, and removing as much as possible of the local neoplasm that evidences the systemic disturbance. But such a procedure should be but a small part of the process of treatment of the cancerous condition. In every case where a malignant neoplasm is removed by the surgeon's knife, there should be the most careful examination of the blood, with full count of the corpuscles both red and white, and differential count of the latter. There should be the closest scrutiny of the patient's habits of living, with notable reference to the diet, the condition of the bowels and kidneys, and the general processes of assimilation and bodily metabolism. Only by attention to these, and the readjustment of the perturbed process of assimilation, can there by any reasonable grounds for hope that the excised neoplasm will not recur.

It is partly because surgeons usually fail to give such attention, that the neoplasm does return after surgical removal in so preponderant a proportion of cases. That it ever fails to recur must be ascribed to the good luck of the patient, or to his chance observation by an internist of discrimination and judgment, rather than to any merit of the average performer of the operation.

I shall have something more to say presently about the preoperative and post-operative treatment of malignant neoplasms, suggesting, among other things, that any surgeon who fails to avail himself of therapeutic measures now available for general treatment of the case in connection with his operations must be

judged guilty of gross negligence, amounting to malpractice. But this presentation of the case may advantageously be delayed until discussion has been had of the new therapeutic measures in question.

SECTION IV

"BIOLOGICAL MEASURES" IN THE TREATMENT OF CANCER

As preliminary to such discussion, it will be well to take a brief survey of various tentatives in the direction of the general treatment of cancer, made in recent years, that have seemed to have scientific foundation and to meet with a certain measure of success in a limited number of cases; to the end that we may inquire whether there is a point of contact between these different kinds of treatment.

The discovery of such a point of contact would obviously give interesting clues to the further investigation of the subject.

The very brief examination necessary in the present connection may advantageously be conducted along the lines of the classification or synopsis given by Bainbridge, who summarizes what he refers to as "biological measures" for the cancer treatment under the following headings: (1) Bacterial toxins, (2) Antitoxic sera, (3) Antitoxins, (4) "Toxins" or "Fluids," (5) Vaccines, (6) Residues, Extracts, and Emulsions, (7) Serous Exudates (Sera), (8) Opotherapeutic measures.

Among the examples of antitoxin, antitoxic sera, and bacterial toxins, the following are named: (1) Blastomycetic antitoxic serum of Sanfelice, based upon the theory that cancer is due to blastomycetes; (2) Wlaeff's Serum, made from cultures of blastomycetes from cancerous inoculated into pigeons; (3) Serum of Emmerich and Scholl, made by inoculating sheep with *Streptococcus erysipelatosus;* (4) Doyen's Serum, from *Micrococcus neoformans;* (5) Schmidt's Serum, from *Mucor mucedo* (Cancroidin, Antimeristem); (6) Wyeth's Toxins of *Streptococcus;* (7) Coley's Fluid—Mixed toxins of *Streptococcus erysipelatosus* and *Bacillus prodigiosus.*

Among the vaccines named are the *Micrococcus Neoformans* Vaccine (Doyen), used in connection with the serum made from the same organism, and the Bacterial Vaccine of Jacob and Geets, made from cultures of the same micrococcus sterilized and standardized according to the opsonic theory.

Residues, Extracts, and Emulsions, include Coca-Gilman Extract, or Emulsion; Vaughan Residue; the Fichera Emulsion, and Autolyzed Cancer or Normal Tissue.

Of serous exudates and body fluids there is a long list, including Hodenpyl's Ascitic Fluid from a cancer subject; Normal human Blood Serum; blood serum of the horse and donkey; Hydrocele Fluid; Spermatocele Fluid; Ascitic Fluid from the subject of alcoholic cirrhosis; Ascitic Fluid from the subject of cardiac insufficiency; and Pleuritic transudate resulting from broken compensation.

Of Opotherapeutic Measures (organotherapy) the examples include (1) "Antituman" of Oestriech made from embryological cartilage and arteries from which a supposedly immunizing substance chondroitin-sulphate is extracted; (2) Thymus Gland Extract; (3) Extract of Sheeps' Thyroids; and (4) Pancreatic enzymes, Trypsin and Amylopsin as widely exploited a few years ago under the auspices of Beard.

As to the status of these various treatments, perhaps I cannot do better than to quote Bainbridge's summary to the effect that: "Many of the agents have been discarded, with practically a consensus of opinion against their efficacy; others continue to receive a certain amount of attention, largely because no definite test of their value has been made upon a convincing basis; while still others are being given careful consideration by a sufficient number of skilled clinicians to warrant the hope that a decision, pro or con, will be soon forthcoming."

I would add, however, that there is a considerable body of evidence to show that a good many of these diverse agents have seemed to produce beneficial effects in a certain number of cases, and that several of them are still actively employed and enthusiastically championed by a number of physicians. Note, for example, the report of Klinger in the *Correspondenz-Blatt für Schweizer Aerzte* for Sept. 23, 1916, on the results obtained with autolysates, to which fuller reference will be made in another connection. That no one of them fully meets the hopes and expectations of its originators may, doubtless, be accepted as fairly demonstrated. But I think it must also be clear that even tentative results would hardly have been attained with so great a variety of animal extracts unless some general principle was involved that gave the different treatments affinity.

It is my belief that the principle in question is the presence of animal or bacterial proteins in all of the various compounds in question. In the case of Beard's Pancreatic Enzymes there are also present digestive ferments closely comparable to those known to be evolved by the white blood corpuscles, the manner of action of which will be dealt with presently.

For the moment, the point that I would emphasize is that the entire group of biological cancer remedies as above outlined comprises agents of very diversified origins that have at least one prominent point of contact in the presence of organic proteins.

If we add that among all the numberless agents that have been used in the general treatment of cancer, there is not one at present commanding the slightest scientific consideration that does not contain protein, we are at least put in the way of an interesting and suggestive line of thought.

The ideas thus engendered are naturally linked with the reflection that many students of cancer have attempted to associate the genesis of the disease with defects of protein assimilation; and also with the very interesting studies of Bulkley in the treatment of cancer by careful regulation of the diet with reference to the protein intake.

The full bearing of the observation, however, is appreciable only when we reflect along the line of the now familiar physiological principle that the introduction of a foreign protein parenterally leads to a development by the body of antibodies to antagonize the toxic influence of that protein; and the further reflection that the antibodies in question are produced by the system in excess of the quantity required merely to neutralize the foreign agent.

A classical illustration of this is found in the use of the antityphoid vaccine, which leads to the production of antibodies in such excess as to give the individual immunity to the typhoid virus for a term of months or years.

A moment's further reflection shows that the antibodies thus produced when a foreign protein is introduced in the body must be of a character to effect the decompounding of the protein molecule. If the thesis of the Proteomorphic theory is accepted, it follows that the introduction of a foreign protein will result in the increased activities of the white and red blood corpuscles and of the organs that produce these corpuscles. Specifically, we may expect that after introduction of a foreign protein there will be observable a modification of the blood count in the direction of an increase of large mononuclear lymphocytes and red blood corpuscles. We may assume that there is a responsive increase in the quantitative enzymic activities of these corpuscles, and that the aggregate effect exceeds the immediate needs of the system as induced by the invading protein.

In other words, there will remain a residual quantity of enzymes in the blood capable of decompounding proteins.

These residual enzymes obviously constitute an agent capable of attacking other foreign proteins, unless we assume that they

are of so specific a character that they can affect only the particular protein that has invoked them.

Have they such specificity?

This, obviously, is an important question. But I think there can be no doubt about the answer. The enzymes that begin the decompounding of the protein molecule are of a tryptic character, closely comparable apparently whether secreted by the digestive glands or by the white corpuscles, and their action is very general. The same enzyme can affect the decompounding of animal and vegetable proteins of the most varied character, as the normal digestion of an ordinary meal in the intestinal tract sufficiently demonstrates. Moreover, it is specifically observed that the white blood corpuscles can attack and destroy bacterial proteins of many types. There are abundant reasons to believe, then, that the enzymes developed as antibodies to any one of the wide range of foreign proteins introduced parenterally may be able to effect the decompounding of other proteins than the particular one introduced.

If, now, we reflect that the cells of a malignant neoplasm are made up of protein which, notwithstanding its close general similarity to that of normal tissues, is in a sense a foreign protein; and, moreover, that these cells because of their newness and rapid growth lack something of the stability of matured normal cells, it is readily explicable that they may be attacked by the protein antibodies in the blood and decompounded.

As suggesting a chemical basis for the expectation that an agent might be developed that would differentiate between normal cells and cancer cells, we may note the researches tending to show that cancer cells have a mineral content in excess of the normal; and, specifically, that the more malignant types of cancer cells are relatively rich in potassium, less malignant ones showing a relative preponderance of calcium; also the fact, to be dealt with in another connection, that cancer tissue is reported as showing only 70 per cent. of the nitrogen content of normal tissue.

If the protein antibodies in the blood come in sufficient quantities, it is even conceivable that the cells of the neoplasm may be altogether dissociated, and the neoplasm itself thus eliminated. But of course so radical a result as this could be expected only in very exceptional cases in which the balance between the normal activities of the corpuscles and the activities of the cells of the neoplasm had not been too profoundly disturbed.

This is perhaps equivalent to saying that success might be expected somewhat in proportion to the stage of advancement of the cancerous condition in general and of the neoplasm in particular.

A highly important complication is found, however, in the fact

that the animal and bacterial foreign proteins now under discussion as furnishing the agents to stimulate the corpuscular enzymes, are in themselves more or less toxic bodies. All foreign serums have elements of toxicity, and this may be so pronounced that the aggregate effect of introduction of the foreign proteins may be the opposite of remedial. As a case in point, the introduction of a foreign blood serum may cause active haemolysis, so that the blood count goes down instead of up. But this, properly interpreted, is in itself an evidence of such activities of a foreign protein as are above postulated, the destruction of the red blood corpuscles evidencing exactly such activities in connection with the elimination of the byproducts of hydrolosis of foreign proteins as is postulated in the Proteomorphic Theory.

But it is obvious that from a therapeutic standpoint the relative toxicity of the protein introduced is of paramount importance. And this observation furnishes the clue to a comprehensive criticism of the entire list of biological agents, above referred to as comprising the various cancer remedies. The bacterial agents employed in making the various serums of Emmerich and Wyeth and Coley are confessedly toxic; and the various and sundry animal serums are all known to have active toxicity when introduced into heterologous parenteral systems.

Hence in practice it happens that in using any of these various vaccines and serums we are introducing agents capable, to some extent, of combating the cancer cell (indirectly), but also agents that put a severe tax on the enzyme-forming organs (blood corpuscles and cytogenic apparatus) they are designed to aid. In using these agents, then, there is always danger that when we take one step up the hill we shall slip back the length of two steps. In other words, while we are by way of "curing" the cancer, we may kill the patient.

As I have already suggested, it is only in a small residual minimum of cases that we can hope to find the balance of nutritional conditions in the system such that, when by a happy chance we stumble on the right dosage of foreign protein, the aggregate results of our effort is beneficial, and the local neoplasm is caused to regress.

Nevertheless, the evidence of these scattered and isolated cases, in the midst of the great mass of failures, is in the highest degree encouraging and enheartening, because, properly interpreted, it tends to establish the general principle that the use of foreign proteins may be of value in the treatment of the cancerous condition. Even though the entire list of "biological remedies" should stand condemned, these tentative remedies will have served a useful purpose in pointing the way to a line of medication which retains their advantages and eliminates their disadvantages.

TABLE I—ORIGINAL CASES UNDER PROTEAL TREATMENT

NINETEEN CASES TABULATED WITH REFERENCE TO THE MINIMUM AND MAXIMUM COUNT OF LARGE MONOCYTES

Case No.	Name	First Count						Later Count						Nature of Case
		Day of Count	Polynuclears	Mononuclears		Eosinophiles	Basophiles	Day of Count	Polynuclears	Mononuclears		Eosinophiles	Basophiles	
				Large	Small					Large	Small			
366	Sr. A.....	106	66	13.5	16	3.5	0.5	135	48	26	24.5	1.5	0	Carcinoma of Breast
278	Mrs. B.....	105	58.6	19.0	20.6	1.6	0	193	54.5	34	11.5	0	0	" " "
369	Mr. B.....	1	51.0	14.0	31.6	2.6	0.6	21	45.3	32	18.3	3.0	1.3	" " "
16	Miss D.....	123	59.0	17.0	24.0	0.0	0.0	198	66.5	21.5	20.0	2.0	0.0	" " "
354	Mrs. M.....	1	73.3	12.6	12.0	1	0	73	60.0	23.0	14.0	2.0	1	" " "
239	Mrs. M.....	141	64.3	16.3	15.6	5.6	0	172	60	23.5	13.0	2.5	1	" " "
258	Mrs. N.....	128	68	14.0	15.3	2.3	0.3	150	58.5	26.5	13.5	1.5	0	" " "
332	Mrs. V.....	0	60	16.0	24.0	0	0	394	39.3	17.6	41.6	1.3	0	" " "
168	Miss W.....	88	66.3	11.6	20	2	0	450	58.6	32.0	8.6	0.6	0	" " "
348	Mr. E.....	0	78.6	10.6	8.3	2.3	0.0	47	66.5	21.0	10.0	2.5	0.0	" " Stomach
153	Mrs. G.....	87	73.0	13.0	12.0	2	0	170	55.0	22.0	20.5	2.5	0	" " Uterus
242	Mrs. S.....	69	60	10.5	29	0.5	0	155	50.5	31	15.5	3.0		Epithelioma of Face
251	Mrs. W.....	61	74.0	11	11	4	...	155	64.5	19.5	12	3.0		Carcinoma of Ovary
322	Mr. N.....	0	74	9	17	0	0	74	51.5	19.5	26.5	2.5	0	Epithelioma of Face
294	Mr. A.....	43	74.6	7.3	18	0	0	64	61	27	8.5	3	0.3	Carcinoma of Throat
309	Dr. G.....	2	75.0	17.0	6.0	2.0	0.0	14	59.0	22.5	16.0	2.5		Sarcoma of Abdomen
381	Mrs. H.....	2	80.5	7.6	8.6	3.3	0	322	67.5	21.5	8.5	0.5	1.5	Melanoma
370	Mrs. R.....	50	74	10	12	3.5	0.5	310	58.4	30.3	5.8	5.4	0.8	Epitheloid Carci. of Hand
163	Mrs. S.....	42	60	15.0	24	1	0	122	61.6	22.5	13.0	2.5	0.5	
Average.....		55.2	67.9	12.9	17	1.9	0.1	169.4	57.1	24.8	15.7	2.1	0.29	
				29.9		2.0				40.5		2.39		

These are cases of inoperable cancer selected primarily because of their clinical interest. All of them showed remarkable progress at the time when the later counts were made. In several cases this progress resulted in clinical recovery; others are still under observation.

The chief interest of the present table lies in the light it throws on modifications of the differential leucocyte count under Proteal treatment, as gauged in connection with the time element. It will be seen that, after this particular group of patients had been under treatment for an average of 55 days, the large monocyte count might be said to be in a static phase, inasmuch as it represented only 12.9 per cent. of the total leucocyte count, which is substantially the percentage noted as the typical average of untreated cancer cases. Yet four months later (on the average) these patients showed such an active response to the continued Proteal treatment that their average large monocyte count was 24.8, not far from double the count of the earlier period. The total mononuclear count had risen from 29.9 to 40.5.

The practical physician will think it not altogether unimportant that the observed microscopical changes harmonize with records of the clinical progress of the cases of inoperable cancer under consideration.

SECTION V

THE EVOLUTION OF THE PROTEIN PRINCIPLE

Charles Darwin was accustomed to emphasize the value of hypothesis as an aid to scientific discovery. This value is, indeed, so evident that the statement of it is almost a truism. Yet it is equally true that a false hypothesis may constitute one of the most hampering of obstacles in the way of progress.

I was forcibly reminded of this, when, a few weeks after the issue of the first edition of the *Monograph* so frequently referred to, I came upon a report that had hitherto escaped my attention, in which an account was given of some very remarkable experiments in the treatment of cancer in the human subject with an alleged "X" substance said to be extracted from thymus of the calf. The report appears in a volume issued by Columbia University Press in the year 1913 captioned "Studies In Cancer and Allied Conditions," and said to be issued from the department of zoology, surgery, clinical pathology, and biological chemistry under the auspices of the George Crocker Special Research Fund at Columbia University.

This is one of a series of volumes with which I had considerable familiarity, but I had failed to note the essential part of the particular report in question; otherwise I should very eagerly have welcomed it as giving support to a quite different theory from the one that the authors of the investigations were pursuing.

The report in question bears title "The Relation of Certain Internal Secretions to Malignant Tumors." The investigation was said to be conducted "with the idea of throwing some light on the relation of some of the internal secretions to malignant tumors." But in point of fact, the part of the report to which I refer has, in my opinion, no essential relations to the subject of internal secretions. The investigation was indeed conducted with the aid of extracts made from the thymus gland; but in my opinion that fact was merely incidental, and precisely the same results would have been attained had the extracts been made from any one of a score of other tissues of the animal body.

In other words, in my opinion—and indeed, in the light of new evidence, I think it hardly open to doubt—the observations made had reference to the results of introducing foreign proteins into the parenteral system, though the authors themselves make it positively clear that they had no such conception. Probably they will repudiate the suggestion now that it is made. Nevertheless I believe the suggestion to be entirely valid.

The results achieved, in the treatment of 49 cases of inoperable cancer in the human subject, were so striking that I shall have occasion to summarize them in a moment, and to make brief quotations from the case records. I shall cite also results attained by Klinger in the treatment of cancer with his animal autolysates, for comparison with the results attained in the use of vegetable proteins. It will be clear, I think, that there is at least a strong presumption—when we note the striking similarity of these independent reports as to the effect on the pain of the cancer subject, on the character of the discharge from the tumor, and on the tumor itself—that a common principle is involved in the three types of therapeutic procedure. And it seems to be scarcely open to question that the most plausible hypothesis—to put the case mildly—as to the character of this common agent is the assumption that it is a protein or a protein derivative.

Had the authors of the paper in question conceived that proteins were indeed the active agent in their remedy, their entire outlook on the subject would have been changed, and in every probability they would have gone forward to perfect a discovery at the verge of which they paused. That they missed the discovery, yet missed it narrowly, is revealed almost pathetically in the summary of conclusion with which they finished their paper, when, following deductions that are not pertinent to the present aspect of the subject, they conclude:

"(3) That there is a substance common to many tissues, but present in varying degrees, which has a positive influence in immunity and cure in animals.

"(4) That the application of these results to the treatment of human tumors results in a temporary improvement in some cases, and in some few cases in an apparent cure.

"(5) That there is still lacking something which will carry improvement observed to a successful issue. In what direction search for such a substance or for an explanation of the problem is to be made is at present unknown."

The concluding sentence makes it unqualifiedly clear that the authors were entirely at sea; that their observations were merely empirical; and that they came to no generalizations that could by any possibility be claimed as constituting the discovery of the protein principle. Had they made such a generalization, the entire history of the cancer problem would have been changed from that moment; and, quite incidentally, my own work in this field would have been unnecessary and would never have been undertaken.

Looking back, in the light of recent developments, it seems strange that the authors should have failed of the prevision, the imagination, that would link their observations one with another

and reveal a unifying principle. But this is the history of every discovery in science when viewed in retrospect. The reader of my *History of Science* will be familiar with numberless instances in point. He will recall that the usual difficulty is that the imagination is hampered by preconceptions of the experimenter based on a false hypothesis of one type or another.

In the present instance, the hampering hypothesis was the thought that the "substance common to many tissues . . . which has a positive influence in immunity and cure in animals," and even in the alleviation of pain in inoperable cancer in the human subject, is an obscure substance, the method of extraction of which was supposed to be known only to a single individual—namely, Dr. Frederick Gwyer, of New York—and which was of so problematical a character that the name "X" substance was given to it. We are told that "the chemistry and method of isolation of this active substance being preeminently the field of Dr. Gwyer, we shall not speak of it." So it appears that the experimenters were working with something which they regarded as mysterious; of which, to be sure, they knew the general origin, but regarding the precise methods of preparation of which they were altogether in the dark.

This was peculiarly unfortunate, both because it savors of an unscientific method of procedure, and because the secrecy in this case probably stood in the way of progress; for it is hardly conceivable that, had the method of extraction employed by Dr. Gwyer been made known to all of the workers, there should not have been some one of them who would have fathomed the open secret,—devining, what the originator of the process doubtless himself altogether failed to surmise, that the "X-substance," interpreted in scientific terms, is merely protein, or a product of partial protein hydrolysis.

But the minds of the operators were under sway of the "X-substance" hypothesis, and hence they were not in the least enlightened when animal tissues various and sundry were subjected to observation "to see if the 'X'-substance is widely spread in tissues or if limited to the thymus," and were informed that it could be found in a great variety of animal tissues. A table is given, naively showing that Dr. Gwyer has extracted—by a method "not yet published"—varying quantities of the "X" substance from macerated human embryo, uterine fibroid, chronic cystic masstitis of the breast, and liver of chronic congestion in the human subject; from muscle, thyroid, thymus, testes, spleen, pituitary, adrenal, and ovary of beef creature; from carcinoma, heart, stomach, spleen, kidney, sarcoma, lung, liver, intestines, and testes of the rat; and from fluid from a carcinomatous cyst,

abdominal ascitic fluid from a tumor, and from carcinoma in the mouse.

Furthermore "Gwyer next examined several of the reported curative agents for cancer and found 'X' substance in all those mentioned, namely (1) Ascitic fluid from a case of stationary carcinoma in the human; (2) calf thymus; (3) sheep thyroid; (4) rat carcinoma tissues prepared after Vaughn's method; and (5) rat carcinoma tissues prepared after the method of Coca and Gilman."

Still another table is published which shows "the interesting fact that immune animals contain more of this 'X' substance than non-immune." It appears from this table that the quantitative differences in question are very slight, the range of variation being given as .011 1/10 to .014⅔ grms. per gram of dried body weight; and we are given no analysis of methods to assure us that these variations do not lie within the limits of experimental errors. The figures serve, nevertheless, to show that Gwyer's tests were apparently not applied for the detection of the full-sized protein molecule as such, but to some derivative product. The fact stands out, however, and from the present standpoint is all-essential, that all the experiments in question deal with tissues or substances rich in proteins. This of course does not by itself establish proteins, as such, as the active agents in the remedial process; but it does raise a strong presumption—taken in connection with the mass of new evidence presented in the present book—that either the protein molecule or one of its derivative products in the form of proteoses, peptones, or polypeptids is the active principle involved. There seems no present need of invoking an "X" substance.

Unfortunately, however, this mysterious substance was invoked, and hence the physicians who administered the treatment were, in their own estimation, performing what was in effect a mysterious rite. If we applaud the freedom from prejudice—altogether unusual in men of their position—that permitted them to employ what they regarded as a secret agent, of unknown method of preparation, in the treatment of a human malady, we must at the same time deprecate their unfortunate thraldom to superstition in focalizing attention on the supposed mysterious agent, when there was every warrant for a simple scientific deduction to the effect that they were really dealing with agents familiar to every physiological chemist.

Be that as it may, however, the mistake was made, and so it unfortunately resulted that, notwithstanding the very interesting and, properly interpreted, important results achieved, nothing of permanency or real significance came of the investigation. It being seen that the magical "X" substance did not ultimately act

with necromatic efficiency, notwithstanding its early promise, the experimenters seemingly abandoned it, and, standing with numerous other agents of similar potency in their hands—had they but known it—they make the bewildered declaration: "That there is still lacking something which will carry the improvement observed to a successful issue"; and, almost wilfully shutting their eyes lest the truth be revealed to them, they add: "In what direction search for such a substance or for an explanation of the problem is to be made is at present not known."

And this bewildered confession of defeat is printed on a page opposite which lies a table telling of really remarkable results achieved in the treatment of human carcinomas and sarcomas, all inoperable and supposedly hopeless, in which two cases were apparently cured; twenty-two cases "greatly improved for a period"; five cases "slightly improved for a period"; and only sixteen cases treated without effect. This table summarizes the text in which we are told explicitly what was the character of the improvement noted. Here are some of the effects: "The tumor becomes gradually smaller, softer, and in some cases ulcerated, and large portions may be sloughed off. In those cases where there has been a large amount of discharge, notably in the uterine cases, this discharge has markedly decreased and in some cases stopped. The pain is relieved to a most remarkable extent; in one case, for example, where morphine was given in doses of 2 grains in twenty-four hours, 5 mms. per day of the extract were sufficient to enable the patient to do without the morphine until her death four months later. Some tumors that were ulcerated on beginning treatment after slight reduction in size became covered with normal epithelium."

It is quite true that the report continues with this statement: "Unfortunately, however, aside from the relief of pain, these results do not persist in all of the cases. The improvement noted goes on from 4 to 8 weeks and then there is a gradual return to the old conditions." But it is added: "The tumor, however, does not grow as fast as would be expected and some of the cases have lived longer than ordinary clinical experience would indicate as the expected period of life." Moreover, detailed case histories are given of a recurrent carcinoma of the breast in which: "The mass grew steadily smaller and after fifteen injections disappeared. There has been no recurrence to date, which is sixteen months after treatment; and of a case of inoperable carcinoma of the corpus of the uterus which became operable under treatment and apparently as a direct result of the treatment, in which the patient was free from recurrence twenty-four months after operation, although she died thirty months after operation, of recurrence, the thymus injection not being kept up after operation."

Viewing such results in retrospect, and recalling that a positive statement is made: "All of the patients treated, 49 in number, have been declared surgically inoperable and the growth positively malignant, both clinically and microscopically," it seems almost incredible that the record of such results, achieved under the auspices of a great university and published with the authentication of an important bureau for cancer research, should have aroused no interest on the part of other workers, and have led to no practical result looking toward the solution of the cancer problem. And I think we must feel that the barrenness of the effort was largely due to the unfortunate hypothesis with which the striking results were linked in the minds of the experimenters and in the minds of the readers of their report.

Here were results attained with an alleged "X" substance of mysterious origin, of unknown composition, a subtsance that no one knew how to duplicate—the private property, as it were, of the physician who had discovered it. Under the circumstances, other searchers in the cancer field probably felt that they could do nothing except await further reports from the alleged discoverer himself; and as these reports were not forthcoming, progress in that direction was at an end. It seems regrettable that some one did not raise the query as to whether the alleged mystery of the "X" substance were not mythical, and, by making similar experiments with thymus extract prepared in a non-mysterious way, following these up with other extracts, carry the experiment forward a step farther along the lines of conquest of cancer.

In point of fact, it appears that at least one experimenter did do this, although whether he knew of the work of the "X" substance experimenters or not I cannot say. I refer to Klinger, the Swiss physician whose work with animal autolysates was referred to in an earlier part of this volume. He, in effect, did precisely what has just been suggested. He tested animal extracts of no mysterious character, using them hypodermically quite as the Columbia University experimenters had used the "X" substance. Like them he produced striking results in the early stage of treatment of cases of inoperable cancer. Like them he saw that it was necessary to find other substances which "will carry the improvement to a successful issue." But, unlike them, he did not feel that "the direction of search for such a substance or for an explanation of the problem was quite unknown." In some way he divined that it might be worth while to test other animal extracts after the efficiency of the first one had been exhausted. In so doing he found that a new term of improvement followed. Thus he was one stage nearer the final goal.

And, as the reader is aware, at the same time that this ex-

tension of methods was being employed by Klinger in Switzerland, my associates and I were working quite independently along precisely similar lines, using vegetable proteins for the most part instead of animal proteins, with strikingly analogous results.

Klinger's results are published in the *Korrespondenz-Blatt für Schweizer Aerzte,* September 23, 1916. A lengthy summary of the article appears in the *Journal of the American Medical Association* for November 4, 1916. No one could fail to note the similarity of the description of Klinger's results with his autolysates to my previously published reports of results obtained with vegetable proteins. For example, he says, as condensed in the *Journal of the American Medical Association:*

"Quite a number of cases have been reported of complete cures or essential improvement under Autolysate treatment of previously inoperable cancer. In Betrand's case an extensive recurrence of a mammary cancer was completely cured. On suspension of the treatment after several months of daily injunction, the tumor began to grow again. The resumption of growth on suspension of the treatment apparently shows that the cure was not a spontaneous subsidence of the tumor but was actually the work of the treatment. Such brilliant results are exceptional. But even in the only improved cases the inflammatory infiltration may subside and the tumor may cast off necrotic masses, the edge of the ulceration healing over. Cancers bleeding and suppurating profusely may have the bleeding and secretion arrested. The tumor often grows so much smaller that the esophagus or the rectum may become permeable once more. Pains caused by the infiltration subside as this retrogresses. In many cases the growth becomes operable after a few weeks of Autolysate treatment."

All this, obviously, might have been written of the effects of administering the vegetable proteins instead of the animal proteins of the autolysates. Note also the following:

"Klinger regards intravenous injection as the most effectual route. There does not seem to be any danger of an anaphylaxis, he says, but sometimes the autolysates seem to lose their power. This can be avoided by changing the material."

The striking analogy here with what has been pointed out in detail again and again in the present book about wearing out the effect of one Proteal and changing to another will be obvious to every reader. Even more striking are the analogies suggested by the theoretical explanation offered as to the action of the autolysates, as follows:

"The results of Klinger's own research and experience confirm the possibility of influencing the growth of a tumor by injecting certain products of the breaking down of albumin. These autolysates supply the body with ready-made ferment while at the same time exerting a stimulating action on the blood-producing

tissues, whipping them up to increased production of the tumor cell-destroying substances. As cancers consist essentially of albuminoid substances, it seems evident that their retrogression and absorption depend on the intensification of certain disintegration processes."

Here, it will be observed, the ideas which furnish the essential thesis of the present monograph—to the effect that protein antigens stimulate the blood-producing tissues, and that these in turn produce the substances that destroy the tumor cell—are stated as if they were matters of common or accepted knowledge. If Klinger reached these conclusions independently, and without having seen my papers of October and November, 1914, and October 2, 1915, his estimate will obviously have peculiar value by way of corroboration.

I mention this, not because questions of priority have considerable significance or even interest, but because the main thesis involved has vast importance, and because the judicious reader cannot fail to be impressed by the fact that certain Swiss physicians working with animal proteins should have obtained results so strikingly in accordance with results obtained by American physicians working with vegetable proteins. It does not appear that Klinger recognizes the response of the blood-forming organs as essentially a protein reaction, but that detracts nothing from the corroborative value of his observations.

My own work has been carried forward, as the reader is well aware, under guidance of an hypothesis—the hypothesis, namely, that results were attained through the administration of proteins or protein by-products, as such; that the patient immunized against one protein may be given a stimulus by the use of another protein, and ultimately by yet another; and that there is nothing mysterious connected with the matter, except in so far as all biological processes are mysterious.

It is vastly important that this thesis should be sustained or repudiated at the earliest possible moment. All my recent experiences tend to confirm the thesis; to establish it more firmly in my mind. In bringing forward the reports of other workers, therefore, as I am doing in the present section, the only thought is to present to the reader as wide an array of evidence as possible, not because there is the remotest element of doubt in my own mind as to the validity of the argument, but because I am aware that the discovery in itself seems so simple as to be almost unbelievable; and because, therefore, I wish to fortify this in the mind of the reader as completely as data at present available permit.

It is a familiar experience in medicine that innovators appear to get results with a remedy that others cannot duplicate. There-

fore, I have wished to show that the protein method is one that is in no wise dependent upon the operation of any individual or company of individuals. I wish to show that any physician can utilize the method and get initial results. I wish also, however, to emphasize the fact that the initial results will not be maintained in the vast majority of cases, if a single protein is adhered to, and that it is necessary to follow up the method along scientific lines, guided by results not only clinical but microscopical (with especial reference to the relative status of the corpuscles); and to point out that this opinion is not the result merely of my own experience, wide though that be, but is fortified by the experience of other workers with proteins, including those who had no definite idea as to the real character of the work they were carrying out.

SECTION VI.

THE PROTEIN RESPONSE INTERPRETED

The paper of October 2, 1915, which announced to the medical profession the introduction of a fundamentally new method in therapeutics,—namely, the use of non-specific protein antigens as such,—as interpreted in the light of the Proteomorphic theory, had to do specifically with the interpretation of the action of non-toxic vegetable proteins in their relation to malignant neoplasms, but clear intimations were given that the therapeutic principle believed to be involved had much wider application. The action of the extract was explained as chiefly due to its protein content (the relatively non-toxic vegetable proteins acting as antigens to stimulate the enzymic activities of the corpuscles and new corpuscle-production by the cytogenic apparatus), and the conclusion was expressly stated that the remedy "is not merely a cancer redemy; it is a remedy against all protein infections."

I further stated the belief that in the attempt to explain the rationale of the action through which the vegetable proteins bring about a beneficent increase in the armies of leucocytes and erythrocytes, "we shall gain glimpses of an entirely new field of therapeutics, and shall be enabled to give at least a proximal explanation of the exact manner of action of a remedy, the introduction of which, I believe, constitutes the inauguration of a method that must in future rank with serum therapy and vaccine therapy—if, indeed, it does not altogether outstrip or totally supplant both these relatively new additions to the equipment of the practical physician."

I have elsewhere referred to the sceptical attitude of the profession toward this confident prophecy. It will be obvious from

the words quoted, however, that in my own mind the matter was perfectly clear. To me it seemed that the Proteomorphic theory offered through basis for interpretation of the observed phenomena. It has been observed that, following the hypodermic injections, in cases of inoperable cancer, pain was modified or annulled, the malodor disappeared, and in many cases the cancer mass itself was modified in character or progressively decreased in size.

I had not only observed these clinical changes at first hand, but had gathered statistical data regarding them (published in detail in a subsequent article in the *New York Medical Journal* of November 13, 1915). As to the facts, there could be no doubt. The explanation of the facts seemed to me equally unequivocal. Scientific caution led me to concede that some other constituent of the plant extract employed—for example, chlorophyll, lipoids, or chromophyl—might in a measure be operative. But the chief action I ascribed unhesitatingly to the protein content; and the explanation was given in terms of the Proteomorphic theory, in part as follows:

It is well known that foreign proteins of whatever character, when introduced into the parenteral system, constitute antigens that stimulate the body to the producion of defensive enzymes, that tend to proteolyze the antigen itself and to neutralize its toxic products. According to the Proteomorphic theory, the chief agents in the production of these proteolytic and antidotal enzymes are the white and red blood corpuscles, the latter being concerned with the end products of the polypeptid order. According to the theory, large numbers of the red corpuscles themselves are destroyed in the liver, in the process of eliminating the toxic end products of protein metabolism from the system. This explains, for example, the pernicious anæmia that may result from the absorption of toxins of protein origin, as in bothriocephalus poisoning.

Similar destruction of the red corpuscles, in their attempt to rid the body of toxins, explains, according to the present thesis, the pernicious anæmia that generally accompanies malignant neoplasms. The animal protein cell does not break down without the production of toxic molecules, and wherever animal proteins of any type are being split up parenterally, such destruction of the red corpuscles must occur, with the result that the cytogenic apparatus may finally be overtaxed and find itself unable to keep up the supply.

It seems probable, however, that vegetable proteins, notwithstanding their chemical similarity to animal proteins, are less likely to produce toxic by-products during disintegration. It is a familiar doctrine that animal proteins rather than vegetable are

the source of intestinal putrefactions. There is theoretical warrant, according to the Proteomorphic theory, for the assumption of the less toxicity of vegetable proteins, in the fact that they doubtless have constituted the food of our ancestors for a much longer period than have animal proteins. Probably the remote ancestors of men were eaters of vegetables for millions of generations before they became eaters of animal foods. And, according to the thesis under discussion, the toxicity of any type of protein is directly proportional to the newness, so to speak, or the infrequency with which the organism has come in contact with it. Toxicity is not a thing *per se,* but a matter of relativity. Inherently, all proteins are poisonous to every organism except the one producing them. A few drops of eel's blood injected into the veins of a dog will cause death.

Doubtless there is great diversity among vegetable proteins themselves as to the matter of toxicity; but the ones actually introduced are of a type to produce a minimum of toxicity while at the same time acting as vigorous antigens, stimulating the cytogenic mechanisms to the rapid production of white and red blood corpuscles. Doubtless these corpuscles proteolyze the vegetable protein itself, but in so doing the red corpuscles are not destroyed in large numbers, because they have a minimum of toxic by-products to deal with.

The large mononuclear leucocytes, which have been shown to produce enzymes that are peculiarly active in the splitting up of cancer cells, are usually found to increase very markedly in the blood. There is also increase of the lymphocytes, which are credited with an active share in the splitting up of animal proteins, and of the eosinophiles. The enzymes generated by these protein fighters begin the disintegration of cancer cells (which, because of their embryonic character, are more susceptible to disintegration than are the cells of normal tissue), and the products of such disintegration are liberated into the blood stream, where the red corpuscles, now banded in adequate numbers, continue the work of proteolysis and elimination.

Of course, the disintegrating cancer cells liberate toxic molecules, and in dealing with these the red corpuscles are of necessity destroyed in large numbers in the liver. But this temporary reduction in the numbers of the erythrocytes is compensated almost immediately by the stimulative effects of a succeeding dose of protein, so that unless the breaking down of cancer tissues goes forward very rapidly indeed, the aggregate count of red cells increases from day to day. It is not unusual to find the count above five million, after the treatment is well established. The enzyme-forming capacity of the red cells is probably increased proportionately.

The chill and rise of temperature that mark the characteristic reaction, and serve as guides to the clinician, probably mark the period when the cumulative action of the leucocytes has taxed the blood with more polypeptid by-products than the red cells can for the moment handle, so that the ranks of the latter have been momentarily depleted, and the chill gives warning that the system is feeling the effects of toxicity. But the rise of temperature is compensatory, since this in itself stimulates the activity of the cytogenic apparatus, so that in a short time there are usually enough of the corpuscular defenders present to take care of the obnoxious protein products.

If compensation does not take place quickly, the delay serves as a warning to the clinician that he should let a longer interval elapse before giving the next dose, or administer the remedy in smaller doses.

If the foregoing reasoning is accepted, it is clear that we can form a tolerably vivid mental picture of the processes through which the regression of the malignant tumor is brought about under the influence of the vegetable protein antigens. The observed phenomenon of the cessation of pain, which is one of the most uniform and gratifying immediate results, is explicable as due to the softening and disintegration of the peripheral cancer cells that have encroached upon the nerve fibrils. The time required for the pain-annulling effects to make themselves manifest would appear to depend upon the exact site of the cancer, and the extent to which its cells have involved the nerves. As the cancer tissue steadily regresses, it is withdrawn more and more from interference with the nerves, and the cessation of pain is lasting.

There is very commonly experienced a sensation of gnawing or digging at the site of the tumor, which is not exactly agreeable, but which the patient cheerfully tolerates because he regards it, doubtless quite correctly, as an evidence that salutary changes are taking place within the tissues of the neoplasm.

The cessation of odor in superficial ulcerative neoplasms or in the discharge from uterine or other masses, is readily understood, according to the present thesis, as due to the activities of the hitherto depleted but now adequate army of red blood corpuscles. The decomposition products that produce the bad odor are precisely of the character of the protein products that, according to hypothesis, the red blood corpuscles deal with habitually. The odor was, therefore, directly due to the inadequacy of the supply of red blood corpuscles, and it disappears almost as a matter of course when this defect is fully compensated.

SECTION VII.

VEGETABLE PROTEINS IN CANCER TREATMENT

It seems perfectly clear, and even obvious now, in the light of later experience, that the above interpretation is valid. But at the time when it was made, the interpretation was fortified by my own belief in the Proteomorphic theory rather than by demonstrative evidence. I was presently able, however, to bring forward substantive evidence of more tangible character through development of a new series of antigens of known composition, made for the express purpose of testing the assumption that the observed action of the original extract above referred to was essentially due to its protein content. An analytical laboratory investigation had been made in which it was shown that each of the twelve constituents contributed a fractional quantity of protein to the extract; but that the major part of the protein came from the mustard seed, as might be expected.

It was at first contemplated to make clinical observations with each of the individual proteins, to determine whether any one of them or any particular combination of them had exceptional value in stimulating a characteristic physiological response of the organism. But since this, obviously, would involve an enormous expenditure of time and labor, it was thought that a short-cut might be effected by making the provisional assumption that any foreign protein of non-toxic character might produce an effective enzymic response. Theoretically, in the light of the Proteomorphic theory, it should be so. I determined to find out whether it was so in practice.

A large variety of vegetable substances were used as the source of new extracts, among others alfalfa seed, alfalfa meal, hemp seed, and rape seed, and, later, clover seed, cotton seed, timothy seed and various others, and sundry foodstuffs.

The practical stimulus to the development of the new proteins was the fact that in a large number of cases patients suffering from inoperable cancer who had responded strikingly to the treatment with the original combination of vegetable proteins came finally to a seemingly static period, at which they showed notable improvement over their previous condition, yet now seemed no longer to respond actively to the stimulus of the remedy. Seemingly they were immunized against further enzymic response to the particular proteins in question. But there seemed to be at least a possibility that they might take on fresh response if new proteins were administered.

This expectation was justified in a considerable number of cases to which the new proteins have been administered, singly or in

combination, during subsequent months. It was found that patients who were virtually immunized to the combined proteins, taking large doses without tangible response, showed marked anaphylactic reaction when small doses of the new proteins were administered. Such being the case, it was not surprising that there should be a corresponding modification of clinical symptoms and a characteristic modification of the differential blood count to which I shall refer more in detail in a moment.

In the *New York Medical Journal* of November 13, 1915, I summarized the preliminary results attained in the treatment of 766 cases of inoperable cancer by 152 physicians using the original vegetable protein extract.

These were all cases of far-advanced malignancy, mostly post-operative. Many of them had been X-rayed and radiumed. All were pronounced inoperable before the protein treatment was undertaken; and this treatment was used to the exclusion of any other. The preliminary results, as tabulated in the article in question, showed that 16.5 per cent. of the cases in question were reported as having died; 19.5 per cent. as being unimproved; and 64 per cent. as being improved to a greater or less extent.

Following the summary, this comment was made:

"As most of the patients in question have been under treatment for periods of only from two weeks to two months; and as by far the greater majority of them were in a very desperate state at the time when the treatment was undertaken, it must be admitted that this is a very gratifying showing. It is perhaps unnecessary to add that, despite the favorable showing, most of these cases are not as yet at a stage where prediction can be made as to the ultimate outcome."

It will be of interest, I think, to introduce here in tabular form a summary of the reports made by a group of co-operating physicians in response to a questionnaire I sent out under date of October 25, 1915. The letter was accompained by a blank form, covering details as to the type of cases of inoperable cancer treated, and the general and special results observed.

This form was sent to about 275 physicians, located in various parts of the United States. In the course of a few days, replies were received from 144 physicians. This was perhaps as high a percentage as could be expected. The number is large enough to give fairly satisfactory statistical data; and there is no reason to believe that the essential character of the report would be changed had the entire number responded. Be that as it may, the reports received are printed here serially, each bearing the number that the physician's name bears in my office files. Results are tentative, but the aggregate report is at least highly suggestive.

Doctor's Serial No.	State of Residence of Physicians. Caps. Show Membership in State Medical Societies; Caps., with Asterisk, Membership in American Medical Association.	Type of Neoplasm and Number of Cases				General Results								Results as to Special Symptoms										
						Unimproved		Improved						Pain		Malodor		General Health		Mental Attitude		Neoplasm		
		Carcinoma	Epithelioma	Sarcoma	Total Cases	Deteriorated	Unchanged	Slightly Improved	Markedly Improved	Good Progress	Out of Danger	Clinically Well	Died	Present	Favorably Modified	Present	Favorably Modified	Uninfluenced	Favorably Modified	Uninfluenced	Favorably Modified	Uninfluenced	Favorably Modified	Marked Reduction in Size
9	Massachusetts	1	..	..	1	..	..	..	..	..	..	..	1	1	1	1	1	..	1	..	1	..	..	..
12	IOWA	2	..	..	2	..	..	..	1	..	..	..	1	2	1	..	..	..	..	..	..	..	1	1
15	Pennsylvania	?	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..
18	PENNSYLVANIA*	11	2	1	14	1	2	4	2	..	..	..	3	8	4	3	2	8	4	3	3	5	2	..
20	MARYLAND*	4	..	..	4	..	..	4	..	..	..	..	..	4	4	4	4	..	4	..	4	..	4	4
22	ILLINOIS*	12	5	..	17	2	4	8	1	..	..	..	2	14	12	8	8	2	15	..	17	3	3	1
25	OHIO	2	2	1	5	..	3	1	1	..	..	..	..	2	1	1	..	3	2	4	1	3	1	1
26	SOUTH CAROLINA	1	1	..	2	..	..	1	..	..	..	..	..	1	1	1	1	..	1	1	..	..	1	1
29	Michigan	1	..	..	1	..	..	..	..	..	..	..	1	1	..	1	..	..	1	..	1	1	..	..
30	CONNECTICUT*	1	..	..	1	..	..	..	..	..	..	..	1	1	1	1	1	..	1	..	1	1	..	..
31	MAINE*	3	..	..	3	..	2	..	..	..	..	..	1	2	..	1	..	3	..	2	1	3	..	..
32	MAINE*	1	..	..	1	..	..	..	..	..	..	..	1	1	1	1	..	..	..	..	..	..	..	..
33	INDIANA*	2	4	..	6	..	..	2	..	3	..	1	..	2	2	1	1	..	6	..	6	..	3	3
34	Maryland	2	..	..	2	1	..	..	..	..	..	..	1	2	..	..	..	1	1	2	..	2	..	..
40	NORTH DAKOTA*	9	..	..	9	..	..	4	4	1	3	..	..	5	5	5	3	..	9	3	6	..	5	4
43	RHODE ISLAND*	1	..	..	1	1	..	..	..	..	..	..	..	1	1	1	..	..	..	..	..	..	..	..
44	CONNECTICUT	1	..	..	1	..	..	1	..	..	..	..	..	..	..	1	1	..	1	..	1	..	1	1
46	NEW JERSEY*	9	2	1	12	4	3	2	..	..	..	..	3	12	1	1	..	11	1	12	..	11	1	..
48	NORTH CAROLINA	1	..	..	1	..	..	..	..	1	..	..	..	1	1	1	1	..	1	1	..	..	1	1
49	PENNSYLVANIA*	2	..	..	2	..	..	..	1	..	..	..	1	2	2	1	1	..	2	..	2	..	1	..
53	West Virginia	1	..	..	1	..	..	..	..	1	..	..	..	..	..	..	..	..	1	..	..	..	1	..
56	Ontario, Canada	2	..	..	2	..	1	..	..	..	..	..	..	2	..	..	..	1	1	1	1	..	1	..
58	INDIANA	13	..	..	13	1	3	1	4	1	..	..	3	13	9	3	3	5	8	4	9	6	3	4
60	PENNSYLVANIA*	1	..	..	1	..	..	1	..	..	..	..	..	1	1	1	1	..	..	..	1	..	..	..
62	TEXAS	1	..	..	1	..	..	1	..	..	..	..	..	1	1	1	1	1	..	..	1	1	..	..
63	Nebraska	1	..	..	1	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
68	Iowa	2	..	..	2	..	..	..	..	2	..	..	..	1	1	1	1	..	2	..	2	..	1	1
72	Massachusetts	1	..	..	1	..	1	..	..	..	..	..	..	1	1	1	1	..	1	..	1	1	1	..
73	Texas	1	..	..	1	..	..	1	..	..	..	..	..	1	1	..	..	..	1	..	1	..	..	1
74	Texas	1	..	..	1	1	..	..	..	..	..	..	..	1	1	1	1	1	..	..	1	1	..	..
75	TEXAS*	1	1	1	3	..	..	..	3	..	..	..	..	2	2	1	1	..	3	..	3	..	3	2

ORIGINAL TABLE OF 284 CASES OF INOPERABLE CANCER TREATED WITH VEGETABLE PROTEIN BY 144 PHYSICIANS—*Continued*

Doctor's Serial No.	State of Residence of Physicians. Caps. Show Membership in State Medical Societies; Caps., with Asterisk, Membership in American Medical Association.	Type of Neoplasm and Number of Cases				General Results								Results as to Special Symptoms											
						Unimproved		Improved						Pain		Malodor		General Health		Mental Attitude		Neoplasm			
		Carcinoma	Epithelioma	Sarcoma	Total Cases	Deteriorated	Unchanged	Slightly Improved	Markedly Improved	Good Progress	Out of Danger	Clinically Well	Died	Present	Favorably Modified	Present	Favorably Modified	Uninfluenced	Favorably Modified	Uninfluenced	Favorably Modified	Uninfluenced	Favorably Modified	Marked Reduction in Size	
76	MISSOURI*	8	..	..	8	..	3	2	3	1	..	..	2	7	7	2	2	2	5	1	7	1	5	2	
77	Tennessee	5	2	1	8	1	1	2	2	2	..	..	..	7	6	6	1	7	0	8	2	4	..	..	
79	Montreal, Canada	2	1	..	3	..	..	1	1	..	..	..	..	2	1	1	0	..	2	1	2	1	..	..	
80	WISCONSIN*	2	..	..	2	..	1	1	..	..	..	..	..	1	1	..	..	..	2	..	2	1	..	..	
82	MONTANA*	1	..	..	1	..	..	..	..	..	..	..	1	1	1	..	..	..	..	..	..	..	..	..	
83	PENNSYLVANIA	1	..	..	1	..	..	..	..	..	..	..	1	..	..	..	..	1	..	1	..	..	..	..	1	
84	NEW JERSEY*	1	..	..	1	..	..	..	..	..	..	..	..	1	1	1	1	..	1	..	1	..	1	..	
85	CONNECTICUT	2	..	..	2	..	..	..	..	..	..	1	1	1	..	1	1	..	2	..	2	..	..	..	1
86	INDIANA*	..	..	1	1	..	..	..	..	..	..	..	1	1	..	1	..	1	..	1	..	1	..	..	
88	TEXAS	1	1	..	2	..	..	..	..	..	1	..	1	2	2	2	2	..	1	..	2	..	2	1	
89	MASSACHUSETTS	..	1	..	1	..	..	..	..	1	..	..	..	1	1	..	..	..	1	..	1	..	1	1	
90	NEW JERSEY*	2	..	..	2	..	..	..	1	..	..	..	1	2	1	..	..	1	1	1	1	1	1	..	
91	Illinois	2	..	..	2	..	..	2	..	..	..	..	..	1	1	2	2	..	2	..	2	..	2	1	
93	ALABAMA*	1	2	..	3	..	..	1	..	2	..	..	..	2	2	2	2	0	3	1	2	..	..	..	
97	Iowa	1	..	..	1	..	..	..	..	..	..	..	1	1	1	..	..	..	1	..	1	..	..	..	
98	Massachusetts	..	1	..	1	1	..	..	..	..	..	..	..	1	..	1	..	..	..	..	..	..	..	..	
100	Ontario, Canada	2	..	..	2	1	..	1	..	..	..	..	..	2	1	1	1	2	..	2	1	1	1	..	
102	COLORADO*	2	..	1	3	..	..	1	2	..	..	..	..	3	3	..	..	..	3	..	3	..	1	..	1
104	NORTH CAROLINA	2	1	..	3	1	..	..	..	2	..	..	..	3	3	1	1	..	3	..	3	..	..	..	3
106	SOUTH DAKOTA*	1	..	..	1	..	..	..	..	1	..	..	..	1	1	1	1	..	1	..	1	..	..	..	1
108	District of Columbia	1	..	..	1	..	..	..	1	..	..	..	..	1	1	1	..	..	1	..	1	..	1	..	1
109	Ohio	1	..	..	1	..	..	..	..	..	1	..	..	1	1	1	1	..	1	..	1	..	1	..	1
111	North Dakota	1	..	..	1	..	..	1	..	..	..	..	..	..	..	..	..	..	1	..	1	..	1	..	..	
118	Michigan	1	1	1	3	..	..	1	2	..	..	..	..	1	1	1	1	..	2	..	3	..	3	..	2
120	KANSAS	..	2	..	2	..	..	1	..	1	..	..	..	2	2	1	1	..	2	..	2	1	1	..	
122	MINNESOTA*	2	1	..	3	..	..	..	3	..	..	..	..	3	3	1	1	..	3	..	2	..	..	..	3
124	NEW YORK*	1	..	..	1	..	..	..	1	..	..	..	..	1	1	..	..	..	1	..	1	..	1	..	1
125	NEW YORK	..	1	..	1	..	1	..	..	..	..	..	..	1	..	1	1	1	..	..	1	1	1	..	1
127	MINNESOTA*	2	..	..	2	1	..	..	1	..	..	..	..	2	2	1	..	..	1	..	..	1	1	..	1
129	SOUTH CAROLINA	2	..	..	2	..	..	1	..	..	..	..	1	2	2	1	1	1	1	1	1	..	2	..	
130	NEW YORK*	1	..	..	1	..	..	..	..	..	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	

132	INDIANA	1	1	..	2	..	..	..	1	1	..	..	..	1	1	1	1	..	2	..	2	..	2	1
135	MASSACHUSETTS*	1	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
138	TEXAS*	1	..	..	1	..	..	1	..	..	..	..	..	1	1	1	1	..	1	..	1	..	1	..
139	CONNECTICUT*	..	..	..	1	..	..	1	..	..	..	..	..	1	1	..	..	..	1	..	..	..	1	..
140	PENNSYLVANIA	1	..	..	1	..	1	..	..	..	..	..	..	1	1	..	..	1	..	1	..	..	..	..
141	Rhode Island	..	..	..	1	..	..	1	..	..	..	..	..	1	1	1	1	..	1	..	1	1	..	..
143	NEBRASKA*	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	1
146	CONNECTICUT*	2	..	..	2	..	..	1	..	..	..	1	1	1	1	1	1	..	1	..	1	..	1	1
150	IOWA*	1	..	..	1	..	..	..	1	..	..	..	1	1	1	..	..	..	1	..	1	..	1	..
155	New York	1	..	..	1	..	..	..	..	1	..	..	..	1	1	..	..	..	1	..	1	..	1	..
159	PENNSYLVANIA	..	..	..	1	..	..	..	..	..	1	..	..	..	1	..	1	..	1	..	1	..	1	..
162	MASSACHUSETTS	1	..	..	1	..	..	..	..	1	..	..	..	1	1	..	..	..	1	..	1	..	..	..
163	Kansas	..	..	1	1	..	..	..	..	..	..	1	..	1	1	1	1	..	1	..	..	..	..	1
169	IOWA*	1	1	..	2	..	1	1	..	1	..	..	..	1	1	1	1	..	1	1	..	..	1	..
170	Maine	..	1	..	1	1	..	..	..	..	..	..	..	..	..	..	..	1	1	..	1	2	..	..
171	NEW YORK*	1	..	..	1	..	..	..	..	..	..	..	..	..	..	1	1	..	..	..	1	1	1	1
173	INDIANA	1	1	1	3	..	..	..	..	3	..	..	1	3	3	2	2	..	3	..	3	..	..	3
176	OHIO*	1	..	..	1	..	..	..	..	..	..	..	1	..	..	..	..	1	..	1	..	1	..	..
182	MASSACHUSETTS*	5	..	..	5	..	2	..	1	1	..	..	1	2	1	..	..	4	1	4	1	2	2	..
186	DISTRICT OF COLUMBIA*	1	..	..	1	1	..	..	..	..	..	..	..	..	..	..	..	1	..	1	..	1	..	..
187	INDIANA*	1	..	..	1	..	..	..	..	..	..	..	1	1	1	..	..	1	..	1	..	..	1	1
188	Arkansas	..	1	..	1	..	..	..	..	..	..	..	..	1	1	1	1	..	..	1	1	..	..	..
192	SOUTH CAROLINA*	1	..	..	1	..	..	..	..	..	..	..	1	1	1	..	..	1	..	..	..	1	1	..
131	Illinois	1	..	..	1	..	1	..	..	..	..	..	..	1	1	1	1	..	1	..	1	1	..	..
185	Ohio	1	..	..	1	..	1	..	..	..	..	..	..	1	..	..	..	1	..	1	..	1	..	..
189	Massachusetts	..	1	..	1	..	1	..	..	..	..	..	..	1	..	1	1	1	..	1	..	1	..	..
194	Ohio	1	..	..	1	..	..	1	..	..	..	..	..	1	1	1	1	1	1	1	1	..	1	1
195	MICHIGAN*	1	..	..	1	..	1	..	..	..	..	..	..	1	1	..	..	1	..	1	1	..	..	..
201	Michigan	..	..	1	1	..	..	..	1	..	..	..	..	1	1	..	..	..	1	..	1	..	..	1
203	MASSACHUSETTS*	1	..	..	1	..	..	1	..	..	..	..	..	..	..	..	..	1	..	1	..	..	..	1
204	Vermont	..	..	1	1	..	..	1	..	..	..	..	..	1	1	..	..	..	1	..	1	..	..	..
205	Ohio	1	1	..	2	..	..	..	2	..	..	..	..	2	2	1	1	..	2	..	2	..	1	..
206	NEW JERSEY*	1	1	..	2	..	..	2	..	..	..	..	..	1	1	1	1	2	..	2	..	..	2	1
208	New Jersey	1	..	..	1	..	..	..	..	1	..	..	..	1	1	1	1	1	1	1	..	..	1	1
209	New York	1	..	..	1	..	..	..	..	..	..	..	1	1	..	1	..	1	..	1	..	..	..	1
210	Missouri	1	..	1	1	..	..	1	..	..	..	..	..	1	1	1	1	1	..	..	1	..	..	..
212	NEW YORK*	..	1	..	1	..	..	1	..	..	..	..	..	..	..	1	1	..	..	1	..	..	..	1
214	NEW YORK	1	..	..	1	..	..	..	1	..	..	..	..	1	1	..	..	..	1	..	..	..	1	..
216	Illinois	1	..	..	1	..	..	..	..	..	..	..	1	1	..	..	..	1	1	..	..	..	..	..
218	WISCONSIN*	2	..	..	2	..	..	..	..	..	..	1	1	1	1	1	..	1	..	..	..	..	1	..
219	NEBRASKA	1	..	..	1	..	..	..	..	..	2	..	1	1	1	1	..	2	2	2	..	2	..	1
220	MASSACHUSETTS*	1	..	..	1	..	..	1	..	..	1	..	..	1	1	1	..	1	..	1	..	1	..	..
225	SOUTH CAROLINA	..	1	..	1	..	..	..	..	..	..	..	1	1	1	1	..	1	..	..	1	..	..	..
227	Illinois	1	..	..	1	..	..	..	..	..	..	..	..	1	..	..	..	..	..	1	..	1	1	1
228	PENNSYLVANIA*	1	..	..	1	..	..	..	..	..	..	..	1	1	1	..	..	1	..	..	1	..	..	..
228	OHIO*	..	1	..	1	..	..	..	1	..	..	..	..	1	1	1	1	..	1	1	..	..	1	..
229	MASSACHUSETTS*	1	..	..	1	..	..	1	..	..	..	..	..	1	1	1	1	..	1	..	1	..	1	..
234	Indiana	..	..	1	1	..	..	1	..	..	..	..	..	1	1	..	..	..	..	..	1	..	1	..
235	Michigan	1	..	..	1	..	..	1	..	..	..	..	..	1	1	..	..	..	1	..	1	..	1	..
236	ARIZONA*	2	1	..	3	..	..	1	..	..	..	1	1	2	2	2	2	..	2	..	2	..	..	2
237	TEXAS	1	..	..	1	..	1	..	..	..	..	..	..	..	..	..	..	1	..	1	..	..	..	..

ORIGINAL TABLE OF 284 CASES OF INOPERABLE CANCER TREATED WITH VEGETABLE PROTEIN BY 144 PHYSICIANS—*Continued*

Doctor's Serial No.	State of Residence of Physicians, Caps. Show Membership in State Medical Societies; Caps., with Asterisk, Membership in American Medical Association.	Type of Neoplasm and Number of Cases				General Results								Results as to Special Symptoms										
						Unimproved		Improved					Died	Pain		Malodor		General Health		Mental Attitude		Neoplasm		
		Carcinoma	Epithelioma	Sarcoma	Total Cases	Deteriorated	Unchanged	Slightly Improved	Markedly Improved	Good Progress	Out of Danger	Clinically Well		Present	Favorably Modified	Present	Favorably Modified	Uninfluenced	Favorably Modified	Uninfluenced	Favorably Modified	Uninfluenced	Favorably Modified	Marked Reduction in Size
238	PENNSYLVANIA	1	..	..	1	..	..	1	..	..	..	..	..	..	..	..	..	..	..	1	..	..	1	..
240	IOWA*	1	..	..	1	..	1	..	..	..	..	..	..	1	1	..	..	..	..	..	1	1	..	..
241	INDIANA*	1	..	..	1	..	..	..	..	..	..	..	1	1	..	..	..	1	1	..	1	..	..	..
244	ALABAMA*	..	1	..	1	..	..	1	..	..	..	..	..	1	1	1	1	..	1	..	1	..	..	..
250	ILLINOIS*	1	..	..	1	..	..	..	1	..	..	..	..	1	1	1	1	..	..	..	1	..	..	..
251	ILLINOIS*	3	..	..	3	..	1	..	..	..	1	2	..	3	3	..	..	1	2	1	2	1	2	1
252	Pennsylvania	..	1	..	1	..	..	..	..	1	..	..	..	..	..	..	..	..	1	1	..	..	1	1
253	NEBRASKA*	1	..	..	1	..	..	1	..	..	..	..	..	1	1	..	..	..	1	..	1	..	1	..
256	TEXAS	1	..	..	1	..	..	1	..	..	..	..	..	1	1	1	1	..	1	..	1	..	..	..
258	MISSOURI*	1	..	..	1	..	1	..	..	..	..	..	..	1	..	..	..	1	..	1	..	1	..	..
260	INDIANA*	..	..	1	1	..	..	..	..	..	..	1	..	1	1	..	..	..	1	..	1	..	..	1
263	New York	..	..	1	1	..	..	..	..	..	..	..	1	1	1	..	..	..	1	1	..	1	..	..
266	IOWA*	1	1	..	2	..	..	2	..	..	..	..	..	1	1	1	1	..	2	..	2	..	2	1
269	Indiana	1	1	..	2	..	..	2	..	..	..	..	..	2	1	1	1	1	1	..	1	..	1	..
271	COLORADO	..	1	..	1	..	..	..	1	..	..	..	..	1	1	..	..	1	..	..	1	..	..	1
272	MISSISSIPPI*	..	..	1	1	..	..	..	1	..	..	..	..	1	1	..	..	..	1	..	1	..	1	1
274	New York	1	..	..	1	..	..	..	..	..	..	..	1	1	1	..	..	..	1	..	1	..	1	..
276	Wisconsin	1	..	..	1	..	..	1	..	..	..	..	..	1	1	..	..	..	1	..	1	1	..	..
278	IDAHO	1	..	..	1	..	..	1	..	..	..	..	..	1	1	1	1	1	..	1	..	..	..	..
279	NEW YORK*	2	..	..	2	..	1	1	..	..	..	..	..	2	1	..	..	..	2	..	2	2	..	..
280	OHIO	1	..	..	1	..	..	..	..	..	..	..	1	1	1	..	..	..	1	..	1	..	..	1
283	NEW YORK*	1	..	..	1	1	..	..	..	..	..	..	..	1	..	1	..	1	..	..	..	1	..	..
285	Maryland	1	..	..	1	..	..	1	..	..	..	..	..	1	1	..	..	1	..	1	..	..	..	..
287	OHIO*	1	..	..	1	..	..	..	1	..	..	..	..	1	1	..	..	..	1	..	1	..	..	1
289	Florida	1	..	..	1	..	..	..	1	..	..	..	..	1	1	..	..	..	1	..	1	..	1	..
290	IOWA*	1	1	..	2	..	..	..	2	..	..	..	..	2	2	2	2	..	2	..	2	..	2	..
292	MISSISSIPPI	1	..	..	1	..	..	..	..	..	..	..	..	1	1	..	..	..	..	..	1	..	..	..
293	INDIANA*	2	..	..	2	..	..	1	1	..	..	..	..	2	1	..	..	..	2	..	2	..	..	..
299	NEW YORK*	..	1	..	1	1	..	..	..	..	..	..	..	1	1	..	..	1	..	1	..	1	..	..
301	Nebraska	..	..	..	1	..	..	1	..	..	..	..	..	1	1	1	1	..	..	1	..	1	1	..
303	TENNESSEE	..	1	..	1	..	..	..	..	..	..	..	1	..	..	1	..	..	..	..	..	..	..	..
304	Vermont	1	1	..	2	..	1	..	1	..	..	..	..	1	..	..	..	..	2	..	1	1	..	..

If we summarize the above table, and condense the findings into a single table aggregating total results, we have the following:

Total number of physicians, 144, residing in 37 states and in several provinces of Canada; including 63 members of the American Medical Association and 29 other physicians who are members of State Medical Associations.

Total number of cases treated, 284; of which 209 were carcinomas, 52 epitheliomas, and 17 sarcomas, 6 being unclassified.

General results of treatment:

(1) Died, 43, or 15.2 per cent. of the total cases.
(2) Unimproved, 60 (21 deteriorated and 39 unchanged), or 21.3 per cent. of total cases.
(3) Improved, 179, or 63.1 per cent.
(4) Of favorable prognosis, out of danger, or clinically well, 48, or 16.2 per cent. of total cases.
(5) Unclassified as to general results, two cases.

Results as to special symptoms:

(1) Pain present in 221 cases; favorably modified by treatment in 171 cases, or 77.4 per cent.
(2) Offensive discharge, present in 111 cases; favorably modified in 96 cases, or 85.6 per cent.
(3) General health of patient: Seemingly uninfluenced by treatment in 77 cases; favorably modified as to appetite, sleeping, color, weight or strength in 180 cases, or 70 per cent.
(4) Mental attitude: Seemingly uninfluenced in 74 cases; favorably modified in 180 cases, or 71 per cent.
(5) Condition of the neoplasm: Seemingly uninfluenced in 79 cases, or 27.8 per cent.; favorably modified in 171, or 60 marked regression in size in 76 cases, or 26.8 per cent.

Dealing, as the statistics do, with supposedly hopeless cases, in the presence of which the physician has hitherto stood powerless, and with symptoms mostly not susceptible of amelioration by any agency hitherto available, this is a showing that is amazing and enheartening.

In the period of thirty months that has elapsed since the reports thus tabulated were received, I have been constantly in touch with a considerable number of physicians who have used the Proteals in the treatment of inoperable cancer. Their reports have come in the form usually of personal letters,—letters not designed in any case for publication, and for the most part written in the interest of the individual patient, asking advice as to some detail of treatment very commonly, and containing expressions of opinion as to the progress of the case of precisely the character a practitioner would make in seeking the advice of a special consultant.

It must be evident, I think, that reports made under such circumstances have peculiar value. In the nature of the case, they are candid, frank, and uncolored.

On the other hand, it must be borne in mind that, by the same token, these men are for the most part not specialists of wide experience in the treatment of cancer cases. A number of them are such, to be sure, but in the main the physicians of the group under consideration are general practitioners. But in a way that makes their testimony all the more important, inasmuch as it shows what the new line of treatment may be expected to accomplish in the hands of the average practitioner. One of the greatest merits of the Proteal treatment is that it enables isolated physicians, in the remotest hamlets, to do something tangible and definite toward ameliorating the condition of the cancer patient who has passed beyond the reach of the surgeon.

Thanks to the new treatment, the most inexperienced practitioner can do more to-day for the amelioration of the condition of a late stage, inoperable cancer case that could hitherto be accomplished by the most experienced practitioner in the best metropolitan cancer hospital.

The substantial unanimity of opinion as to the character of results attained in their own practice by some hundreds of physicians scattered about the country, and in foreign countries, is so striking a phenomenon that it is susceptible of but one interpretation. It is impossible that all these men should be mistaken. Their individual observations, when aggregated, pile mountain high the evidence that the proteal treatment has remarkable effect in relieving pain of the inoperable cancer subject; removing the bad odor of cancerous discharges; improving the general health of the patient; and conspicuously modifying the condition of the malignant neoplasm.

After carefully scrutinizing the evidence, it is difficult to avoid the conclusion that these beneficial effects of the proteal treatment, in varying degree, may be observed in an overwhelming proportion (not less, in my opinion, than 80 per cent.) of cases of inoperable cancer, wherever located, in which the remedy is administered in suitable doses.

This, it will be observed, postulates nothing as to the ultimate effects of the treatment. It says nothing as to the "cure" of cancer. As to that, I shall have something to say in detail a little later. Here it suffices to note that the records under consideration tell of definite and unequivocal improvement of the most tangible character in a large proportion of cases; such improvement amounting in a certain number of cases to seeming clinical recovery.

SECTION VIII

THE BLOOD IN CANCER SUBJECTS

It will be recalled by those who have read the original presentation of the Proteomorphic Theory that the theory ascribes to the lymphocytes in the blood the function of beginning the decompounding of protein molecules. It will be recalled also that experiments (of Vaughan) are cited which seem to show that the large monocytes have power to produce enzymes that bring about the decompounding of cancer cells.

It is of pecular interest, then, to inquire as to the modifications of the blood count that are associated with the cancerous condition, and the further modifications that are brought about by therapeutic application of protein antigens.

It has long been recognized by pathologists that there are marked modifications of the blood count in nearly all cases of malignant disease. Most observers have been content to note the reduction of the hæmoglobin index and of the red blood count, and the marked leucocytosis that usually characterizes the condition, at least in its advanced stages. A number of observers, however, have fortunately made more elaborate studies, and records are available in the literature covering a considerable body of cases in which complete blood counts were made that furnished the basis for a comparative study in connection with the original observations that I am about to record.

Dr. Price Jones has published detailed results of the study of 29 cases of cancer, including carcinomas of the breast, stomach, intestine, generative organs, tongue, and larynx, and variously located sarcomata. His results show an average of 3,838,000 red blood cells and 10,409 white cells to the cubic millimeter. The differential count showed 73.7 per cent. of polynuclears, 10.38 per cent. large monocytes, and 13.6 small lymphocytes. Eosinophiles and basophiles are not recorded, but by exclusion are shown in the aggregate to represent 2.32 per cent. of the leucocyte census.

Another interesting series of cases comprises cancer in which there were bone matastases, recorded by different observers, and aggregating 22 cases fully reported. Here the average red blood count was found to be 2,808,000; the average white blood count, 14,214 (increased by the presence of a few cases in which the leucocytosis was extreme). The differential count shows 58.11 per cent. polynuclears; 14.89 per cent. large monocytes; 25.86 per cent. small lymphocytes; 0.87 per cent. eosinophiles; and .027 per cent. basophiles. A considerably modified average is found if we consider only the first count in each of the 22 cases, the result being: red corpuscles, 2,744,000; white corpuscles, 11,500

(the aberrant case being omitted); polynuclears, 65 per cent.; large monocytes, 11.7 per cent.; small lymphocytes, 22 per cent.; eosinophiles, 1 per cent.

These results may be compared with the table, herewith presented, of our own untreated cases. It will be seen that there is close general agreement. I would call special attention to the

TABLE II—THE BLOOD COUNT IN CANCER

TWENTY-NINE CASES OF DR. PRICE JONES AT THE MIDDLESEX HOSPITAL, ENGLAND

Nature of Case	No. of Cases	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears	
					Large	Small
Cancer of the Breast	9	4,230,000	10,400	7,115	1,324	1,661
Carci. of the Stomach	7	3,770,000	9,700	7,070	835	1,598
" of the Intestine	2	4,600,000	14,600	11,478	1,446	1,490
" Generative Organs	5	4,160,000	14,280	10,038	1,671	2,103
" of the Tongue	1	3,780,000	18,600	13,974	1,711	2,845
" of the Larynx	1	2,400,000	6,300	4,365	819	1,091
Sarcoma	4	4,490,000	10,930	7,847	1,158	1,694
Weighted averaged of 29 cases	.....	3,838,000	10,409	7,664 73.7%	1,077 10.38%	1,421 13.6%

TABLE III—TWENTY-TWO CASES OF CANCER WITH BONE METASTASES REPORTED BY DIFFERENT PHYSICIANS

Observer	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
					Large	Small		
1. Hawley	75	3,172,000	7,300	63.0	10.0	27.0	0	0
2. Harrington	62	2,751,000	2,500	56.4	20.0	19.6	1.6	0
3. Houston	49	2,300,000	6,700	54.0	9.2	36.2	0.6	0
4. Parkes	...	1,056,000	10,200	78.0	9.5	11.0	1.5	0
5. Harrington	35	1,600,000	14,000	63.0	17.6	16.7	0.7	0
6. Parmentier	60	1,940,000	3,500	60.0	14.0	21.0	4.0	0
7. Wolfer	15	1,550,000	20,000	66.0	12.0	22.0	0	0
8. Kurpjuweit	25	1,825,000	9,100	48.5	31.4	19.2	1.0	0
9. Kurpjuweit	60	4,320,000	19,700	86.1	7.0	6.2	0.7	0
10. Frese	21	900,000	9,220	64.5	19.0	15.0	1.0	0.5
11. Schleip	40	1,984,000	16,400	82.0	3.7	8.2	1.2	0
12. Schleip	105	4,452,000	7,600	58.6	4.6	35.1	0.8	1.6
13. Nægeli	46	2,168,000	6,000	66.0	8.2	19.0	0	0
14. Ward	65	4,760,000	10,800	50.7	17.4	31.2	0.6	0
15. Ward	50	4,920,000	9,000	68.9	6.5	23.3	0.8	0.5
16. Ward	115	4,725,000	3,700	51.0	4.6	42.2	0.4	1.8
17. Ward	85	5,615,000	8,500	68.0	11.4	21.4	0.2	0
18. Ward	56	3,850,000	20,300	60.0	14.0	23.0	3.0	0
19. Kast	...	3,020,000	120,000	96.17	1.25	2.16	0.42	0
20. Turnbull	45	2,150,000	22,000	59.0	8.5	31.0	1.0	0.5
21. Hirschfeld	20	1,000,000	30,000	78.8	15.6	4.6	0.5	0
22. Bloch	50	3,000,000	6,000	56.7	12.7	30.5	0.1	0
	53.3	2,744,000	11,500	65.26	11.7	22.06	1.0	0.2

column showing the percentages of large mononuclear leucocytes. Recalling that in normal blood the large monocytes number only 2 or 3 per cent., as a rule, with perhaps 5 per cent. as maximum, it will be noted that in Price Jones' series of cases these cells number 10.35 per cent. of all leucocytes; in 22 cases of bone metasta-

ses, as first counted, they number 11.7 per cent.; in one of our series (26 cases) they number 13.5 per cent., and in another of our series (22 cases) they number 14.05 per cent. It should be understood that the large mononuclear leucocytes do not constitute a homogenous group. They include, in an ordinary cancer case, not only large lymphocytes and normal large monocytes (the macro-

TABLE IV—ORIGINAL CASES

THE BLOOD COUNT IN 26 UNTREATED CASES OF INOPERABLE CANCER

Case No.	Name	Nature of Case	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
							Large	Small		
346	Mrs. C.....	Carci. of Breast.....	90	4,630,000	9,320	63	12	25	0	0
361	Mr. C.....	" " Jaw.....	90	4,568,000	6,230	77	9.6	13	.3	0
378	Mrs. DeB..	" " Uterus.....	100	4,272,000	8,000	57	18.3	21.6	3	0
335	Miss D....	" " Breast.....	80	2,464,000	10,650	70.6	8.6	7.6	2.6	0.3
310	Mr. E.....	" " Bladder.....	65	3,920,000	....	82	11	6	1	0
394	Mrs. L.....	" " Breast.....	100	5,280,000	9,500	65.5	10	20	4	0.5
349	Mrs. G.....	" " Uterus.....	95	4,564,000	7,700	46.6	13.6	39	.6	0
333	Mrs. H.....	" " Breast.....	85	3,824,000	8,650	50	19	28	3	0
316	Mr. K.....	Epithe. of Palate.....	75	4,096,000	....	61	23	15	1	0
356	Mr. L.....	Carci. of Stomach.....	85	4,640,000	9,880	75.5	12.3	12.3	0	0
375	Miss Mc...	" " Breast.....	90	3,872,000	7,880	70.6	13.3	14.6	1.3	0
327	Miss M....	" " Mediastinum..	90	5,160,000	9,220	64	12.6	21.6	1.6	0
358	Mr. U.....	Sarc. of Peritoneum.....	95	5,272,000	7,550	52.5	20.75	21.5	4.75	0.5
224	Mrs. S.....	Epithelioma.....	95	5,088,000	9,000	78	13	6.5	2.5	0
325	Mr. S.....	Carci. of Larynx.....	85	4,288,000	7,240	77	8	15	0	0
344	Mrs. S.....	" " Breast.....	90	4,684,000	9,220	80.6	12.6	6.6	0	0
362	Mrs. St....	" " Cœcum.....	85	4,016,000	8,100	71.3	13	15	0	0.6
331	Mr. S.....	Mixed Parotid Cancer...	70	3,744,000	9,780	67	10	23	0	0
312	Mrs. Y....	Carci. of Uterus.....	45	2,730,000	16,600	66	16	16	2	0
355	Mrs. S.....	" " Intestine.....	85	3,376,000	8,660	74.3	14.3	10.3	1.3	0
	Mr. M.....	Doubtful Diagnosis.....	45	1,424,000	11,550	68	8	22	2	0
341	Mr. G.....	Carci. of Uterus.....	90	5,360,000	8,430	57	20	21.5	1.5	0
	Dr. L.....		100	4,096,000	10,000	67	13.5	9.5	10.	0
	Dr. Mc G..					79.3	9	6.6	4.6	0
	Mr. P.....	Ep. of Tongue.....	95	4,992,000	9,800	62	9	22	7	0
339	Mrs. T....	Carci. of Stomach.....	85	4,920,000	9,680	53.3	21.3	25	0.3	0
Average for above 26 cases.....			84.4	4,258,000	9,240	67.5	13.5	17	2	.07
Average for 22 cases in Table VI.....			81.9	4,271,000	8,840	67.95	14.05	16	1.69	.07
Weighted averages for 48 cases.....			83.2	4,264,000	9,080	67.72	13.77	16.6	1.8	.07
Unweighted " " 99 "			73.2	3,777,000	10,000	68.6	12.45	17.16	1.56	.11

The above 26 blood counts of cases of inoperable cancer constitute a fairly representative group, presented here together because they chance to be cases in which only a single blood count was made. They are otherwise unselected. The averages of this group may advantageously be compared with those of a second group of untreated cases detailed in Table VI. A combination of these charts gives the averages for 48 untreated cases of inoperable cancer. For purposes of comparison, the averages of the 29 cases of Price Jones and the 22 cases of bone metastases reported by various investigators are also presented. It will be seen that there is close general agreement. The relatively low red corpuscle count in the bone cases may perhaps be due in part to direct involvement of the marrow. The Price Jones cases were hospital cases. The original cases were ambulatory, although late stage inoperables. Thus we have a fairly representative group of 99 cases, and, in so far as any generalizations are justified from so small a number, we may take the grand average as suggesting a typical blood picture in advanced stages of the cancerous condition.

phages of Metchnikoff), but myeloctyes (neutrophile, eosinophile, and occasionally basophile), leucoblasts, and lymphoidocytes. For the moment, however, it will be convenient to group all of these together, in consideration of their probable similarity of origin, and their obvious similarity of structure.

Striking the (unweighed) average for these 99 cases, we find the large mononuclears (of these various groups) aggregated to represent 12.45 per cent. of the total leucocyte count. This is about two and a half times the normal maximum percentage; and it would appear that we may accept some such modification as this of the large monocyte count as typical of advanced cases of malignant neoplasms. Individual cases, as a matter of course, show exceptions, but there appear not to be more than five or six cases in the entire 99 in which the count of large monocytes was found as low as the normal maximum limit.

We are justified, then, I think, in regarding a marked increase of the large monocytes as a typical manifestation of the presence of malignant neoplasms in an advanced stage. These clinical observations in the human subject find support, it may be added, in Price Jones' observations of cancerous mice in which also a very marked increase of the large monocytes was noted. It should be observed, however, as having interest in another connection, that the percentage of large monocytes in the blood of the normal mouse is far higher than in the human subject. The figures given by Price Jones are, for normal mice, 21.5 per cent.; for cancerous mice 32.2 per cent. of the total leucocyte count.

The question at once arises as to whether the observed increase of large monocytes in the cancerous condition is to be regarded as a part of the disease process, or whether, on the other hand, it manifests a salutary modification indicating nature's attempt to combat the invasion of the lawless cancer cells.

In view of the known functions of the leucocytes in guarding the body against bacterial invasions, we may, I think, unhesitatingly accept the increase of leucocytes in general in the cancerous condition, and of the large monocytes in particular, as representing a salutary process. The fact that Vaughan's experiments showed that enzymes produced by the large monocytes bring about at least partial decompounding of cancer cells naturally comes to mind in considering the observed fact of the increase of these monocytes in the cancer subject.

It seems at least a justifiable inference that the presence of the cancer cells has directly stimulated the production of large monocytes, just as the presence of foreign pathogenic bacteria stimulates the increased production of phagocytic polymorphs.

If this view is accepted, it is permissable to suppose that in a very large number of cases incipient malignant neoplasms are nipped in the bud, so to speak, by the activities of the large monocytes; and that the presence of a tangible cancer demonstrates the fact that, in this individual case, the body has been unable to produce the defending corpuscles in adequate numbers to overmaster the invading cancer cells; although, at the same time, it must be

observed that the presence of the increased number of monocytes shows that the bodily organism has not given up the fight.

The Blood Count as Modified by Protein Antigens

When charts, based on the study of original cases, showing the results of such blood counts in about 150 original cases under

TABLE V—ORIGINAL CASES

48 Unselected Cases After an Average Period of 102 Days of Protein Treatment.

Case No.	Name	Nature of Case	No. of Days	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
								Large	Small		
106	Miss A...	Thyroid	195	100	5,376,000	8,000	61.5	20	15	3.5	0
311	Mrs. A...	Thyroid	4	90	5,250,000		56.5	19	22.5	2	0
	Miss A...	Thyroid		100	4,480,000	6,700	58	13.5	23	4.5	1
271	Mrs. B...	Sarcoma	16	65	3,328,000	10,250	79.3	8.3	10.6	1.6	0
223	Mrs. B...	C. of Uterus	69	85	4,064,000		80.6	10.6	8.6	.6	0
	Mr. B...	Tuberculosis	40	90	5,600,000	8,400	45.5	35	10	4	.5
	Fr. B...	Diabetes		95	5,296,000	8,100	55.6	20	20.3	3.3	.6
135	Mrs. B...	Carci. of Breast	84				67	16	16	1	0
133	Miss D...	Thyroid	184	100	5,632,000	6,400	55.5	24.5	18.5	1.5	0
167	Mrs. D...	Carci. of Breast	73	85	4,370,000		66	18	14	2	0
8	Miss D...	Thyroid	205	90	4,032,000	6,500	43	24.5	29	3.5	0
192	Mrs. D...	Carci. of Breast	18	85		9,620	64.3	15	17.3	3.3	0
353	Miss E...	Thyroid	59	90	4,640,000	7,300	58.5	24	16.5	1	0
305	Mrs. E...	Carci. of Breast	15	80	2,848,000		77.6	13.6	5	3.6	0
88	Miss F...	Thyroid	211	100	5,440,000	8,000	60	20	18.5	.5	0
209	Mr. F...	Ep. of Tongue	150	100	5,600,000	7,700	70	14.5	13	2	.5
186	Mrs. G...	Thyroid	90	85	3,976,000	9,340	57	8.3	33.3	.3	0
261	Mrs. G...	C. of Uterus	52	85	5,000,000		72	11.6	12.6	3.6	0
250	Mrs. H...	Thyroid	144	95	4,032,000	7,200	47.5	24	25	2.5	0
	Mrs. H...	C. of Intestine		80	4,032,000	11,300	67	13	18	1	1
221	Mr. H...	C. of Œsophagus	65		5,320,000		74	13.3	11.6	1	0
	Miss K...	Thyroid		90	4,490,000	7,220	62	23	13	2	0
395	Mr. K...	Indigestion	61	100	5,440,000	7,100	62.5	14	18.5	5	0
307	Mrs. K...	C. of Uterus	63	75	3,840,000		68	11	20.5	.5	0
48	Mrs. L...	Thyroid	114		5,296,000	5,720	50	15	35	0	0
326	Miss L...	Thyroid	75	100	4,928,000	6,600	62	22.5	14.5	1	0
207	Mrs. L...	Int. Toxæmia	96	90	4,040,000	8,300	52	15.6	24.6	7.6	0
372	Miss McG	Thyroid	98	100	4,576,000	9,200	55	20	16.5	8	.5
40	Mrs. M...	Thyroid	201	95	4,524,000	7,100	49	19.5	26	5.5	0
165	Sr. M...	C. of Breast	101	100	4,960,000	6,300	52.5	21.5	24.5	1.5	0
264	Mr. N...	" " Œsophagus	351	75	4,028,000		59.6	20	9.3	1	0
283	Mrs. Q...	" " Breast	34	90	4,784,000		62	23	14	1	0
259	Mr. R...	Toxaemia	137	100	5,308,000	6,400	77	14	7.5	1	.5
268	Mrs. S...	Endoth. of Throat	52	95			62.5	24	12.5	1	0
274	Mrs. S...	Carci. of Uterus	38	70	3,400,000		84	4	8.6	2.6	.6
281	Mr. S...	Sarc. Testicle	42	70	2,168,000		68.5	11.5	14	6	0
298	Mrs. S...	Carci. of Breast	19	80	3,856,000		70	11.6	10	2.6	0
43	Mrs. S...	Thyroid	131	84	4,160,000	7,930	62	12	26	0	0
24	Mrs. S...	Carci. of Breast	113	90	5,450,000	7,800	64	14	21	1	0
208	Mrs. T...	Thyroid	98	90	4,496,000	8,330	61.25	15.5	18	3.75	1.5
159	Mr. V...	C. Mediastinum	75		4,620,000		78.5	15	6	.5	0
407	Mr. W...		60	100	5,664,000	7,000	77	9	13	1	0
25	Mr. W...	Thyroid	215	100	5,728,000	9,000	68	15	16.5	0.5	0
32	Miss W...	Thyroid	220	95	4,250,000	7,600	73	11	15	1	0
47	Mr. W...	C. of Tongue	119	80	3,440,000	10,250	77.6	13.3	6.3	2.6	0
247	Mrs. Wn	C. of Breast	62	65	3,804,000		63.5	15.5	18.0	2.	0
382	Mr. Wk..	Exophthalmus	60	95	5,324,000	7,500	44.3	30.3	23.5	2.3	0
44	Mrs. D..	Rheumatoid Arthritis	196	95	4,444,000	6,700	54	25	16.5	4.5	0
	Average		102	89	4,673,000	7,830	63.4	16.9	16.8	2.33	.1

protein treatment were available, it was at once evident that there were very striking and characteristic modifications of the differential count coincident with the administration of the vegetable proteins; and that these were curiously similar to changes coincident with the administration of an anti-thyroid serum.

A typical, yet somewhat extreme, case, for example, was that of a patient suffering from carcinoma of the throat whose blood on the 8th of October, 1915, at an early stage of the treatment showed 7.3 per cent. of large mononuclears to 18 per cent. of small ones; and whose count about six weeks later (on the 22nd of November) was almost precisely reversed as regards these particular elements, showing 18.3 per cent. of large mononuclears to 7.6 per cent. of small ones.

Other specific cases show the proportion between large and small mononuclears as follows: 19 to 20.6 at an early stage of treatment and 34 to 11.5 at a later stage; 14 to 31.6 at an early stage, and 27.75 to 15 at a later stage; 9 to 16 at an early stage, and 21.5 to 8 at a later stage; and 10.5 to 29 at an early stage, against 31 to 15.5 after three months of treatment.

A typical thyroid case showed the balance between large and small mononuclears as 8 to 19.6 on the 12th of October, and shifted to 25 to 19.5 on the 17th of December, after two months of use of anti-thyroid serum.

It seems a fair inference that, since vegetable proteins on one hand and anti-thyroid sheep serum on the other produce precisely the same results in human subjects that Vaughan observed in case of the sheep inoculated with cancer tissue, the principle involved is the response to the protein antigen as such rather than a specific response to any particular type of protein.

This, it will be observed, would be fully in keeping with the assumption that the mononuclear leucocytes are the agents chiefly involved in beginning the decompounding of foreign proteins in general when brought in contact with the blood.

Be the theoretical explanation what it may, however, the thing that has peculiar significance in the present connection is the observed fact that the hypodermic administration of proteins (independent of any other treatment) has been demonstrated to bring about a very marked modification of the leucocyte count, in the direction of the increase of the large mononuclears. Cases in which no favorable modifications of this kind have taken place under Proteal treatment have not been observed to make favorable clinical progress.

Fairly typical of desired results in case number 348, who on the 15th of October (before beginning treatment) had a hæmoglobin index of 80 per cent., a red count of 3,168,000, a white count of 9,880; with 78.6 poly., 10.6 large monocytes and 8.3 small lymphocytes; and who on the 1st of December showed a hæmoglobin index of 90 per cent., a red count of 4,944,000, and a white count of 7,500; with 66.5 per cent. poly., 21 per cent. large monocytes, and 10 per cent. small lymphocytes.

TABLE VI—ORIGINAL CASES

Blood Count in 22 Cases of Inoperable Cancer Before Treatment

Case No.	Name	Nature of Case	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
							Large	Small		
369	Mrs. B. . . .	Carci. of Breast.	90–95	4,480,000	8,220	51	14	31.6	2.6	.6
368	Mrs. C. . . .	" " "	90	3,976,000	9,330	65.6	14.3	17.3	2.3	.3
360	Mr. D.	Epithe. of Jaw.	90	3,776,000	7,880	51	17.5	23.5	7.75	.25
345	Mr. D.	Carci. of Larynx.	90	4,668,000	8,350	79	15	6	0	0
309	Dr. G.	Sarc. Abdomen.	. . .	5,056,000	. . . .	75	17	6	2	0
381	Mrs. H. . . .	Melanoma.	100	4,752,000	7,600	80.5	7.6	8.6	3.3	0
313	Mrs. K. . . .	Carci. of Breast.	90	4,960,000	. . . .	61.5	23.5	14	1	0
354	Mrs. M. . . .	" " "	95	5,064,000	8,150	73.3	12.6	13	1	0
359	Mrs. Mc. . .	" " "	90	3,608,000	9,100	63.6	16.3	18	2	0
322	Mr. N.	Epithe. of Face.	60	3,212,000	. . . .	74	9	17	0	0
371	Miss N. . . .	Carci. of Breast.	90–95	4,456,000	7,900	65	15.6	16.3	3	0
332	Miss V. . . .	" " "	85	5,008,000	8,880	64	16	24	0	0
317	Miss W. . . .	" " "	85	4,137,000	. . . .	66.6	14.3	20.6	.6	.6
348	Mr. E.	" " Stomach.	80	3,168,000	9,880	78.6	10.6	8.3	2.3	0
314	Mr. Mc. . . .	Epithe. of Mouth.	90	4,704,000	5,250	74	15	11	0	0
376	Mrs. T. . . .	Car. Gall Bladder.	85	4,600,000	8,300	70.3	12	15.2	2	0.3
301	Mrs. B. . . .	Carci. of Larynx.	80	4,200,000	. . . .	48	18	31	0	0
348	Mr. E.	" " Stomach.	80	3,168,000	9,880	78.6	10	8.3	2.3	0
287	Mr. H.	Sarc. of Testicle.	80	3,592,000	13,500	81.6	7	11.3	0	0
399	Mrs. M. . . .	Carci. of Breast.	95	5,120,000	9,300	75.5	15	8.5	1	0
374	Mr. T.	Sarc. of Jaw.	85	4,130,000	10,000	53.6	15.6	23.3	3.3	0.3
317	Miss W.	Carc. of Breast.	85	4,137,000	. . . .	63.6	14.3	20.6	0.6	0.6
	Average.		81.9	4,271,000	8,840	67.95	14.05	16	1.69	.07

The Same 22 Cases After an Average Period of 41 Days of Proteal Treatment

Case No.	Name	Nature of Case	No. of Days	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
								Large	Small		
369	Mrs. B. . . .	Carci. of Breast.	21	100	5,724,000	6,500	45.3	32	18.3	3	1.3
368	Mrs. C. . . .	" " "	29	95	4,112,000	8,500	64.6	19	12.3	3.6	.3
360	Mr. D.	Ep. of Jaw.	39	95	4,384,000	6,600	52.6	17.3	20.6	9	.3
345	Mr. D.	Carci. of Larynx.	21	90	4,720,000	7,880	73	16.6	5	4.6	0
309	Dr. G.	Sarc. of Abdomen. . .	14	. . .	3,412,000	7,850	59	22.5	16	2.5	0
381	Mrs. H. . . .	Melanoma.	30	100	4,500,000	8,200	81	12.5	5	1	.5
313	Mrs. K. . . .	Carci. of Breast.	80	100	5,564,000	8,000	60	19.3	17.3	3.3	0
354	Mrs. M. . . .	" " "	73	100	5,500,000	7,800	60	23	14	2	1
359	Mrs. Mc. . .	" " "	57	100	4,384,000	7,200	59	16.5	19	4.5	.5
322	Mr. N.	Ep. of Face.	74	85	4,192,000	7,700	51.5	19.5	26.5	2.5	0
371	Miss N. . . .	Carci. of Breast.	34	95	4,352,000	8,600	59.5	16.5	21	3	0
332	Miss V. . . .	" " "	90	100	5,656,000	8,900	48.5	27	20.5	4	0
317	Miss W. . . .	" " "	38	85	4,944,000	7,330	56.6	21	18.6	3.6	.3
348	Mr. E.	" " Stomach . . .	47	90	4,944,000	7,500	66.5	21	10	2.5	0
314	Mr. Mc. . . .	Ep. of Mouth.	31	85	4,888,000	8,650	68.3	19.3	11.6	.6	0
376	Mrs. T. . . .	C. Gall Bladder.	62	100	4,896,000	9,600	62	15.5	19.5	2.0	0
301	Mrs. B. . . .	Carci. of Larynx.	32	90	3,724,000	7,270	75	14	11	0	0
348	Mr. E.	" " Stomach . . .	48	90	4,944,000	7,500	66.5	21	10	2.5	0
287	Mr. H.	Sarc. of Testicle.	4	85	3,256,000	8,500	73	12.3	14.0	0.6	0
399	Mrs. M. . . .	Carci. of Breast.	8	100	4,896,000	9,500	69.5	14.5	13.5	1.5	0
374	Mr. T.	Sarc. of Jaw.	32	95	4,864,000	8,300	70.5	18.	6.	5.5	0
317	Miss W. . . .	Carci. of Breast.	35	85	4,944,000	7,330	56	21	18.6	3.3	0.3
	Average.		40.4	93.5	4,667,000	8,000	62.6	19.05	14.94	2.95	0.2

Modification of the blood count following the administration of fairly vigorous Proteal treatment. Particular attention is called to the notable increase in the large mononuclears. Such a modification is certainly one of the most characteristic, and perhaps the most important, of the changes brought about by the proteal treatment. Note also the increase in hæmoglobin and in red corpuscles, and the decrease in white corpuscles as a whole and in the percentage of polynuclears.

These cases are grouped together simply because they are cases in which an original blood count, made before treatment, was supplemented by a subsequent count after treatment. They are otherwise quite unselected, and are strictly comparable to the cases shown in the earlier chart. The blood picture of the treated cases shows wide departure from the type-picture supplied by the 99 untreated cases.

The average results of fourteen unselected cases under the protein treatment are summarized thus: At the beginning of treatment hæmoglobin index 89 per cent., red corpuscles 4,500,000, white blood corpuscles 8,878; with 68 per cent. polymorphs; 14.9 per cent. large monocytes; 14 per cent. small lymphocytes; .65 per cent. eosinophiles; and 0.32 basophiles. At a later stage after an average of 42 days of protein treatment, hæmoglobin index 96 per cent.; red corpuscles 4,930,000, and white blood corpuscles 8,107; with 62 per cent. polymorphs; 18 per cent. large monocytes; and 16 per cent. small lymphocytes; 3 per cent. eosinophiles; and 0.35 basophiles.

Some Practical Hints

It is almost axiomatic to say that observation of the blood count must in future be regarded as indispensable as a guide to dosage and frequency of administration in carrying out the proteal treatment of cancer. This is particularly true, however, after treatment has been continued for a period of five or six weeks.

Up to that time, there is almost certain to be favorable progress of the case if the remedy is pressed pretty actively from the outset, the doses being carried to the point of securing a pronounced general reaction on at least one occasion, and subsequently modified so that there is a mild reaction.

During this stage, there will usually be observed a pronounced increase of red blood corpuscles; but this is no more notable than the lymphocytosis, with marked preponderance of the large cells.

It should be observed, however, that the activities of the monocytes in beginning the decompounding of cancer cells may be so great as to put so severe a tax on the energies of the red blood corpuscles that their numbers will be for a time materially reduced, even when the case is progressing favorably.

A very good illustration of this is furnished by case 309, in which there was a large abdominal sarcoma located near the spine, which had been declared irremovable after an exploratory incision. On the 19th of September, 1915, two days after beginning the Autolysin treatment, this patient showed a red blood count of 5,066,000; with 75 per cent. polymorphs, 17 per cent. large monocytes; 6 per cent. small lymphocytes and 2 per cent. eosinophiles. Two weeks later the red blood count had decreased 3,412,000; but in the meantime the polynuclears had decreased to 59 per cent.; there being now 22.5 per cent. large monocytes, 16 per cent. small lymphocytes, and 2.5 per cent. eosinophiles.

Taken by itself, the decrease in red blood corpuscles might seem alarming; but that the above interpretation of this decrease is correct is suggested by the fact that the patient went ahead stead-

ily and rapidly to clinical recovery with apparent entire regression and disappearance of the tumor, so far as could be determined by palpation. The case was supposed to be hopeless by the surgeon who attempted the operation; yet progress was so spectacular under the protein treatment (exclusively) that a few weeks later the patient returned to his home and took up once more his accustomed work as a practising physician.

Such a reduction in the red blood corpuscles under the Proteal treatment as that just noted would be regarded with equanimity, however, only where there was, as in the instance cited, a large tumor mass undergoing rapid disintegration. And even then, it is questionable whether, as a rule, it would be desirable to carry forward the disintegration of the tumor mass so rapidly as to produce a marked reduction in the red blood corpuscles. A better way, ordinarily, would be to regulate the dosage so as to secure only such amount of hydrolysis of cancer cells as can be dealt with by the red blood corpuscles without reducing their ranks much below the five-million mark.

Cases are reported where the dosage of proteins was pressed so actively from the outset that the breaking down of a pelvic cancer was effected so rapidly that the system could hardly have been expected to withstand the shock had there not been opportunity for exterior discharge and drainage. One physician described the results attained in such a case as reminding him of the effects of a curette, so rapid was the removal by exfoliation of the cancer tissue.

In such a case, there is obvious danger of severe hemorrhage. This danger would be obviated, at least in a measure, if the dosage were so regulated that the decompounding of the cancer cells was less rapid.

I have elsewhere pointed out that the critical period in the treatment of cancer cases comes after an interval of several weeks, when the systemic response has been carried to the maximum. Almost invariably, the question then arises as to the best manner of continuing treatment, in order that the effects may be cumulative, and the case carried to the favorable termination that seemed promised by the early response.

It is now that constant appeal should be made to the microscope to determine the precise status of the red blood corpuscles and the various leucocytes. An endeavor should be made to keep the former as near as possible to the five-million mark; while it is to be hoped that the lymphocytes will continue to represent at least one-third of the leucocyte count, and that the large mononuclears will outnumber the small ones.

A typical satisfactory blood count is shown by patient number 239 (carcinoma of the breast), whose blood on the 8th of Janu-

ary, 1916, after about six months' treatment, showed 100 per cent. hæmoglobin, 5,096,000 red blood corpuscles, and 8,000 leucocytes with 60 per cent. polys., 23.5 large monocytes; 13 per cent. small lymphocytes; 2.5 eosinophiles, and 1 per cent. basophiles.

At the time when this count was made, the patient was steadily progressing, and she went ahead to seemingly complete clinical recovery.

TABLE VII—ORIGINAL CASES

THIRTY-ONE UNSELECTED CASES OF INOPERABLE CANCER AT EARLIER AND LATER STAGES OF PROTEIN TREATMENT

FIRST COUNT AFTER AN AVERAGE PERIOD OF NINETY DAYS OF TREATMENT

Case No.	Nature	Nature of Case	No. of Days	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
								Large	Small		
294	Dr. A.	Ep. of Tongue	43	95	4,864,000	7,330	74.6	7.3	18	0	0
366	Sr. A.	C. of Breast	106	95	4,448,000	8,200	66	13.5	16	3.75	.5
278	Mrs. B.	" "	105	90	4,400,000	..	58.6	19	20.6	1.6	0
16	Miss D.	" "	123	90	4,464,000	..	59	17	24	0	0
153	Mrs. G.	" Uterus	87	88	4,656,000	..	73	13	12	0	0
263	Mrs. H.	" "	126	90	3,744,000	7,500	58	20	20	2	0
270	Mrs. H.	" Breast	5	...	....	..	73	17	9	1	0
94	Mrs. H.	Ep. Forehead	190	95	5,160,000	8,300	55	26	14	4.5	.5
233	Mrs. L.	C. of Breast	28	...	4,680,000	..	65	19.5	15	.5	0
239	Mrs. M.	" "	141	90	3,376,000	7,200	64.3	16.3	15.6	3.6	0
131	Mrs. N.	" Uterus	171	100	5,964,000	7,600	62	18.6	18.3	1	0
258	Mrs. N.	" Breast	47	90	5,330,000	..	59	18	23	0	0
248	Mr. O.	Sarc. of Test	72	85	4,352,000	..	71	9	16	.3	0
235	Mr. P.	C. of Jaw	65	...	4,352,000	..	68.3	14	9	4	0
64	Mr. P.	Ep. of Cheek	115	80	4,240,000	..	72	9.5	18.5	0	0
149	Mrs. R.	C. of Breast	79	86	4,570,000	..	63.5	21	15.5	0	0
370	Mrs. R.	" Skin	5	95	4,896,000	10,200	72.6	14	10.6	2.6	0
84	Miss R.	Chond-Sarc	170	95	5,128,000	10,200	71.75	11.5	16.25	.5	0
289	Mrs. S.	C. of Breast	38	90	4,616,000	..	51.5	20	25	3.5	0
242	Mrs. S.	Ep. of Face	69	75	2,800,000	..	60	10.5	29	.5	0
138	Mrs. F. S.	Sarc. of Phar	129	85	3,554,000	9,000	56.3	17	24.3	2.3	0
163	Mrs. S.	C. of Breast	21	75	4,226,000	..	65	20	15	0	0
347	Mrs. S.	" "	90	75	4,280,000	8,440	42	28	30	0	0
193	Mr. S.	" Jaw	165	100	3,936,000	7,600	58	19.5	20	1.5	0
280	Mrs. S.	" Thyroid	159	100	4,460,000	7,200	74	15.6	6.6	4	0
296	Mr. Von E.	Sarc. of Leg	24	90	4,730,000	..	54	20	26	0	0
23	Miss W.	C. of Breast	124	80	4,440,000	..	60	13	27	0	0
168	Miss W.	" "	88	80	4,448,000	..	66.3	11.6	20	2	0
251	Mrs. W.	" "	63	85	3,570,000	..	74	11	11	4	0
189	Mr. M.	" Rectum	83	80	4,312,000	..	77.6	11.6	10.6	0.6	0
391	Mrs. W.	" Ovary	60	100	4,116,000	8,800	52.0	25.5	14	8.0	.5
		Average	90	88.5	4,400,000	8,270	63.69	16.37	17.72	1.7	.05

This table may advantageously be compared with earlier tables showing blood condition in untreated cancer cases, and with the table on the opposite page, showing later history of the same cases.

It will be of interest to contrast this blood count with another, No. 399, which chanced to be made on the same day, in which the hæmoglobin test was also 100 per cent. and in which the red blood count was 4,896,000, but in which the leucocyte count was 9,500 (more than could be desired), polymorphs representing 69.5 per cent., and large monocytes, only 14.5 per cent., as against 14.5 per cent. small lymphocytes, together with 1.5 per cent. eosinophiles and 1 per cent. basophiles.

Here, it will be observed, there is substantial uniformity between the two counts except as regards three factors: namely (1) the total leucocyte count, which was 9,500 in the second patient against 8,000 in the first; (2) the polynuclear count, which was 69.5 against 60; and (3) the large monocyte count which was 14.5 against 23.5. These differences, however, are highly significant, in view of the studies of the blood count above outlined.

TABLE VIII—ORIGINAL CASES

THE SAME 31 UNSELECTED CASES AFTER AN AVERAGE OF 152 DAYS OF PROTEIN TREATMENT

Case No.	Name	Nature of Case	No. of Days	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
								Large	Small		
294	Dr. A.....	Ep. of Tongue.....	87	90	5,288,000	9,800	73	18.3	7.6	2.6	1
366	Sr. A.....	C. of Breast.....	134	100	4,160,000	6,700	48	26	24.5	1.5	0
278	Mrs. B....	" " "	193	100	4,832,000	6,100	54.5	34	11.5	0	0
16	Miss D....	" " "	215	100	5,252,000	7,500	61.5	13	24	1.5	0
153	Mrs. G....	" " Uterus.....	170	90	3,840,000	7,500	55	22	20.5	2.5	0
263	Mrs. H....	" " "	142	100	3,424,000	7,700	72.5	10	15.5	2	0
270	Mrs. H....	" " Breast.....	122	95	5,696,000	6,800	72.5	17.5	5.5	4	0
94	Mrs. H....	Ep. Forehead.....	209	95	5,240,000	8,000	58.5	18	21.5	2	0
233	Mrs. L....	C. of Breast.....	165	100	5,652,000	8,600	76.5	13.5	8.5	1	.5
239	Mrs. M....	" " "	172	100	5,096,000	8,000	60	23.5	13	2.5	1
131	Mrs. N....	" " Uterus.....	207	95	5,124,000	8,300	62	20.5	16.0	1.5	0
258	Mrs. N....	" " Breast.....	150	100	4,800,000	9,400	58.5	26.5	13.5	1.5	
248	Mr. O.....	Sarc. Testicle.....	162	90	5,404,000	8,300	71.5	20.5	8	0	0
235	Mr. P.....	C. of Jaw.....	91	90	5,200,000	8,880	87.6	7.3	4.6	.3	0
64	Mr. P.....	Ep. of Cheek.....	190	90	3,904,000	11,700	84	10.5	4.5	1	0
149	Mrs. R....	C. of Breast.....	169	100	5,600,000	6,800	74	13.5	9.5	3	0
370	Mrs. R....	" " Skin.....	67	90	4,130,000	12,000	77.5	15	6.5	1	0
84	Miss R....	Chond-Sarc.....	206	100	4,928,000	10,000	57	13.5	28	1.5	0
289	Mrs. S....	C. of Breast.....	134	100	5,184,000	7,300	61.5	16	20	2.5	0
242	Mrs. S....	Ep. of Face.....	155	100	4,672,000	7,200	50.5	31	15.5	3	0
138	Mrs. F. S..	Sarc. of Phar.....	188	95	4,640,000	8,000	53	11	32.5	2.5	0
163	Mrs. S....	C. of Breast.....	102	100	4,928,000	7,000	61.5	22.5	13	2.5	.5
347	Mrs. S....	" " "	86	60	2,326,000	10,500	40	19	39	1	1
193	Mr. S.....	" " Jaw.....	175	100	4,376,000	6,900	60	16.5	21	1.5	1
280	Mrs. S....	" " Thyroid.....	174	100	5,200,000	7,400	72	18	7	2.5	.5
296	Mr. Von E.	Sarc. of Leg.....	118	100	4,640,000	7,800	60.5	20	14.5	4.5	.5
23	Miss W....	C. of Breast.....	217	100	4,960,000	9,000	72	16	9	2.5	.5
168	Miss W....	" " "	180	100	5,650,000	9,200	64.5	18	17	.5	0
251	Mrs. W....	" " "	155	95	4,288,000	8,600	64.5	19.5	18.6	3.3	.3
189	Mr. M.....	" " Rectum	91	80	4,072,000	7,520	69.3	11.6	18.6	.3	0
391	Mrs. W....	" " Ovary.....	93	95	5,632,000	8,100	54	25	17.5	3.5	0
	Average.....		152	95.5	4,782,000	8,270	64.4	18.3	15.6	1.9	0.2

Comparison with the preceding table will show characteristic progress during this period of fourth and fifth months (on the average) of Proteal treatment.

Nothing more would have been necessary to make the two counts identical as to their leucocyte percentage balance than to take the 9.5 per cent. in excess of polymorphs in the second case and transfer them to the large monocyte column. I am greatly disposed to believe that had the Proteal treatment been able to effect such a modification of blood count, there would have been a modification in the production of the leucocytic enzymes that might have turned the scale in the patient's favor. As it was, however, the second patient developed a small metastasis in the neck while undergoing the treatment, which so alarmed her that

she went to another city for X-ray treatment. A few months later her death was reported.

What might have been the progress of the case had the Proteal treatment been continued is of course only conjectural. But the blood count showed that the case was not progressing under the proteals as satisfactorily as could be desired; whereas the blood count of the other patient gave every warrant for the favorable prognosis that was presently justified.

Incidentally we may note that both these cases were cancers of the breast.

In another connection, I have suggested that when a patient under the Proteal treatment has been carried to a stage of very marked improvement, progress may be retarded by excessive dose, putting a tax upon the corpuscles that is not compensated by further stimulus to the blood-forming organs. Obviously, the guide as to this must be found in the blood count.

In general, I would suggest that when the red-cell count has been brought to approximately five millions, and the differential leucocyte count to the status above suggested, in which there is marked lymphocytosis with distinct preponderance of the large mononuclears, the physician should be chary of giving large doses of protein.

It may be desirable to discontinue treatment altogether for a time; but it is usually preferable to restrict the size of dosage, and extend the intervals between doses. A dose of 5 or 10 minims given weekly or semi-weekly may keep the corpuscular response at a maximum, and foster progress that would be impossible under larger or more frequent doses. Yet the same case may have required dosage of 40 or 50 minims daily or on alternate days at an earlier stage.

All therapeutic rules have exceptions, however; so I must add that it appears sometimes to be advantageous to give a patient who has reached the static period the shock of a large dose, or of an intravenous injection, which produces a vigorous reaction. A case was recently reported in which, quite by accident, part of a dose was given into a vein. There was anaphylactic reaction within a few minutes, and subsequently the neoplasm began rapidly to regress, although it had for some weeks been static, after having passed through an earlier stage of favorable progress.

All this, however, only emphasizes the point made in an earlier section, to the effect that any one who can administer a hypodermic injection may begin the proteal treatment of a case of cancer, and for a time secure gratifying results; but that, even in cases that have larger possibilities, these possibilities can be realized only when the subsequent administration of the remedy is carried forward along scientific lines. One object of the present

section has been to suggest that the scientific administration in question necessarily connotes repeated observation of the blood count as modified by the administration of the proteal antigens.

SECTION IX.

CANCER AND THE LYMPHOID SYSTEM

There is one profoundly important aspect of the problem of treating cancer with proteins to which incidental reference has been made in this monograph, but which, so far as I am aware, has never been elsewhere suggested.

The point in question is this: Every cancer patient has been subjected to a spontaneous course of protein treatment before he comes into the hands of the surgeon or physician.

Such, at least, must be considered the fact if the thesis as to the nature of cancer that furnishes the basis of this monograph is accepted. According to that thesis, as elsewhere elaborated, there is incessant warfare from the outset between the blood corpuscles and the neoplastic cells, with the consequent destruction of combatants on both sides.

If the corpuscles win, the lawless cells are entirely eliminated, and no tangible neoplasm will result.

But if the new cells win, they ultimately constitute an aggregate that we call a tangible cancer. Meantime, there has been an effort on the part of the bodily defenders—namely, the white and red corpuscles—that has profoundly disturbed their status as health-defending agents. And needless to say this profound disturbance has extended to the organs that produce the blood corpuscles,—namely the bone marrow, the lymphatic system, and the spleen. Abundant proof of this is found in the presence of myelocytes, normoblasts, and abnormal lymphoid corpuscles in the blood stream.

The manner of change that brings about this modification of the blood conditions may be illustrated by a quotation from Dr. Ward's book on *Bedside Hæmatology*. In the chapter on "Generalized Affections of Blood-forming Tissues"—in which there is no specific reference to cancer—he says:

"It is well known that the most powerful and efficient stimulants of blood regeneration are the products of blood destruction. This is well shown in the case of Addisonian [pernicious] anæmia and in the results of injections of very small quantities of blood in cases of anæmia. We need not then be surprised if after this destruction we find excessive formation. We do, as a matter of fact, find both excessive formation of white cells and the pres-

ence of the products of excessive destruction in the urine. The next step in the pathology will be the reversion of the cell-forming organs to a more primitive type as a result of the continued strain on them. This also we find in lymphæmia as we do in Addisonian anæmia. Here, however, the analogy ends for the reversion in the case of lymphæmia may proceed in the extent of resurrecting tissues whose cell-forming days were over."

Elsewhere in the same chapter, the salient aspect of the subject is elaborated as follows:

"In the group of diseases now to be discussed the common and distinctive feature is involvement of all the blood-forming organs by a growth or overgrowth that is similar in each organ.

"In the first sub-group, the leukæmias, not only the adult blood-forming organs, marrow, spleen, and lymph glands are effected but in other situations tumors may appear which are composed of tissue identical with that in the marrow, etc. These tissues are the embryonic and infantile blood-forming organs, the liver and thymus, and, secondly, connective tissue wherever met with. This extraordinarily wide distribution of lesions in some cases is the more readily explained when we remember that all mesoblastic tissue is potentially blood-forming—*i.e.*, blood-cell-forming—just as it is potentially sarcomatous or fibromatous."

To understand the subsequent sequence of events, we have to recall that overstimulation of any organ leads presently to exhaustion. So the same stimulus that at first produces an excess of blood corpuscles may presently result in marked decrease. Note, for example, what Pappenheim says as to this:

"Leucopenia is not diametrically opposed to hyperleucocytosis even when it appears from the first as a leucopenia, e.g., in typhoid. It ought rather to be regarded as differing in degree only, since high degrees of leucocytosis, or leucocytosis of long standing, may merge into leucopenia. When this occurs, especially if accompanied by the presence of early forms [leucoblasts, myelocytes, normoblasts] in the blood, it indicates commencing exhaustion of the overtaxed bone marrow."

Such are the recognized effects of a persistent stimulation of the organs of blood regeneration by the products of blood destruction. It must be obvious, then, that in every far-advanced case of cancer, or at any rate in every case in which a neoplasm has assumed considerable proportions, there must be a greater or less degree of what Ward refers to as "hyperprophy of the lymphocyte-forming tissues," including spleen and marrow. According to the present thesis, the increased formation of lymphocytes and early myelogenous forms in response to the stimulus of the cancer cells is a salutary process,—an attempt on the part of the organism at spontaneous cure of the malady. But the net result, when the new growth is too active, is that ultimately the organs of blood-formation have reached their maximum response

to that particular antigen, and through prolonged overstimulation a general myelogenous and lymphatic maladjustment is produced which is in many respects comparable to the general leukæmias of different origin. "Many people," says Ward, "consider that leukæmia is of the nature of a malignant growth as, for instance, cancer of the stomach is a malignant growth." Again he says: "That there are analogies between cancer and the leukæmias no one will deny." He adds that in his opinion these analogies are not sufficient to bring the two into the same class; admitting at the same time that theories in the matter are at present only tentative, and going on to say that: "If leukæmias are cancer, then the metastases of cancer are not due to emboli from a primary growth nor to spread by direct continuity along lymphatics, but are primarily formed in each situation in which they occur under the influence of the same stimulus that produced the original tumor." To be sure, Ward thinks that most pathologists will not subscribe to this view of cancer metastases, and so will reject the analogy which suggests that leukæmia is to be regarded as a form of new growth of the bone marrow or glands. He adds, however, that "the theory and the analogy form a fascinating and possibly productive field for discussion and research."

There is no occasion here to enter into detailed discussion of the pathological questions involved. My object in referring to it is to emphasize the view that the presence of a cancerous growth implies a profound dyscrasia of the lymphoid tissues. There is of course nothing new in this view, although it may perhaps be said that there is novelty in the explanation of the fact just offered,—the suggestion, namely, that the lymphatic hypertrophy may be a direct result of the response to the antigenic stimulus of the decompounding cancer cells.

From a practical standpoint, the importance of the matter lies in the fact that a full recognition of the conditions will prevent anyone from supposing that he has effectively treated a case of cancer when he has merely removed a local neoplasm.

More specifically, the matter is important in the present connection as emphasizing the view that a cancer patient, before he comes into the hands of the physician, has undergone a radical course of protein treatment. This fact is immensely significant in its bearing on the practicalities of a subsequent course of protein treatment at the hands of the physician.

If the view just presented is accepted, for example, it becomes obvious that any further treatment based on the administration of cancer proteins (and such treatment has been suggested and extensively tested) would be illogical in the highest degree. All that cancer proteins can accomplish as antigens has already been accomplished, and the net result is that the patient still has a

neoplasm associated with a responsive dyscrasia of the blood-forming organs. Hence the futility of the autolysate treatment of Fichera and allied attempts to treat cancee with so-called" "vaccines" made from the tissue of neoplasms.

A disturbance of the blood count, or a deviation from the normal, in token of cytogenic dyscrasia, may be expected as a matter of course. If the neoplasm is small, as in case of a epithelioma of the mouth, the antigenic stimulus of the cancer cells may be of so relatively slight a character that the blood picture, at the time when the patient comes under observation, may be identical with that which has been presented in an earlier chapter as typically favorable. The red blood count may be above five million; the white count about 8,000; and the mononuclears may constitute 35 or 40 per cent of the leucocytes with a preponderance of large monocytes; and there may be relatively high percentage of eosinophiles.

This would indicate, according to the present thesis, that the patient in question is receiving spontaneous protein treatment that is accomplishing valuable results in retarding the progress of the malady.

More commonly, however, as records of our counts have shown, the patient at the time of first examination has reached a stage at which the corpuscular balance is much less favorable. The stimulus to the cytogenic apparatus (in particular the bone marrow), followed by exhaustion, is revealed in a relative monocypenia, but with marked preponderance of the small lymphocytes, associated with a deficiency of eosinophiles, and, usually, with a marked decrease of the red corpuscles. Commonly there is marked general leucocytosis, but with preponderance of the polynuclears. Myelocytes, leucoblasts, and normoblasts may be present in greater or less profusion. The polynuclear commonly show marked deviations from the normal as regards the conformation of the nucleus (S-shaped nucleus, ring-form, spiral contortion, etc.), with in general a marked tendency toward "progression to the left,"—speaking in terms of the Arneth formula.

This peiture suggests that a spontaneous cancer-antigen treatment has passed its maximum of efficiency, and that relatively rapid and unfavorable progress of the neoplasm must now be expected unless a new and different stimulus can be brought to bear on the defensive mechanism of the body.

Such a new stimulus may be supplied by the X-ray, by radium, or by the administration of proteins of a type quite different from the proteins of cancer.

In discussing the action of X-ray and radium elsewhere I have suggested that the beneficial effect of these rays may be in part at least due to their general influence on the blood count. I wish

now to emphasize this aspect of the matter in the light of the statement above quoted from Ward to the effect that: "It is well known that the most powerful and efficient stimulants of blood regeneration are the products of blood destruction."

I am inclined to think that a large measure of the benefits sometimes unquestionably attained in cancer from the use of X-ray and radium may be explained as due to their destructive influence on the blood corpuscles. It is well known that in general leukæmias, the number of white corpuscles may be reduced by X-ray treatment. It is also known that radium exercises a destructive influence on the blood corpuscles. It follows that these influences must stimulate the blood-forming mechanism, inasmuch as their use tends to saturate the blood, more or less, with "the products of blood destruction."

In point of fact, I have observed that patients that had undergone X-ray or radium treatment before applying for Proteal treatment sometimes show a blood picture precisely of the kind that we have come to regard as favorable, and as indicating the best possible response to the proteal treatment itself. I am strongly inclined to the opinion that in many cases this favorable blood picture is directly due to the use of X-ray or radium, and that the beneficial effects of these treatments are in a large measure due to this general modification of the blood quite as much as to any local effect on the neoplasm.

Indeed I think it is an open question whether it may not be possible to get the good effects of X-ray or radium by treatment applied generally, or to the bones or to the spleen, rather than by prolonged application to the site of the neoplasm itself. This, however, is a matter that need not be discussed in detail in the present connection. It suffices to emphasize the opinion that prolonged exposure to X-ray or radium at the site of the neoplasm is inadvisable; and that the danger of local burns, with their characteristically disagreeable and resistent ulcers, may be obviated without sacrificing any of the expected benefits, by shifting the locus of treatment.

Incidentally, it may be noted as a matter of interest that radium, when introduced into the animal organism, is believed to have something like an elective affinity for the bone marrow, taking permanent lodgment there. So, at least, I have been informed by one of the most experienced workers in this field, who stated this as a matter of fact, quite without reference to any theory as to the action of radium on the blood-forming mechanism.

It is the commonly accepted opinion of pathologists that, whereas the X-ray exerts a temporarily beneficial effect in the treatment of leukæmias, the effects cease to be cumulative after a time, and ultimately the beneficial response ceases, and the patient goes

on to a period of decline, which the X-ray now seems powerless to retard.

We must expect, I think, that the same thing will ordinarily be true of the X-ray or radium treatment of the type of lymphæmia or myelæmia associated with the presence of malignant neoplasms. It was above suggested that the neoplasm assumes significant proportions only when the blood-forming mechanism has ceased to respond effectively to the antigenic stimulus of the cancer proteins. When this has occurred, a new stimulus may be given to the blood-forming apparatus by X-ray or radium treatment. In a certain number of cases, this new stimulus may be sufficient to turn the scale in favor of the bodily defenders, and against the neoplasm; with the result that the lawless cells are totally disintegrated, and a condition of at least clinical cure is effected. But in a much larger proportion of cases, it cannot be hoped that the new stimulus given by the radiation treatment will serve to turn the tide so effectively. In a vast preponderance of cases, the neoplasm will be found to be so thoroughly fortified that it offers successful resistence to the best fighting equipment that the body can develop under the new stimulus.

Even where the local neoplasm seems completely to disappear under the new stimulus, it is a matter of unfortunate observation that either direct or metastatic recurrences presently reveal themselves, showing that the profound lymphatic dyscrasia, however modified, has not been eliminated.

In such a case (and this is equivalent to saying, in practically all cases of cancer), it is desirable to seek still other methods of stimulating the cytogenic apparatus, and thus further to fortify the fighting equipment of the body. The therapeutic agents available for this purpose include: (1) Hygienic measures, such as proper food, exercise, massage, and cold baths; and (2) An indefinite series of foreign proteins, animal, bacterial, and vegetable.

SECTION X.

ANIMAL EXPERIMENTATION AND PROTEAL THERAPY

About the year 1908 workers at the Loomis Laboratory were experimenting with transplantable tumors in dogs. They found that with dogs, as with rats and mice, some individuals seemed immune to the transplantation of such tumors. In other cases, the tumor after transplantation grows for a time and then "spontaneously" regresses. In yet others, it continues to grow until it brings about the death of the animal. As with

rats and mice, the dog that had recovered through "spontaneous" regression of a tumor appeared to be immune to subsequent transplantation.

It occurred to the experimenters to test the effect of transfusing the blood of such an immunized animal into the vascular system of a dog in which the transplanted tumor was progressing. Experiments were first made with the blood serum of the immunized dog; and the results were negative. But when, subsequently, transfusion was made of the whole blood of the dog, a curative result was observed, the tumor in the affected animal regressing, and the dog going on to complete recovery.

It seemed fairly obvious, then, that there was something in the entire blood of the animal that was not conveyed with the serum alone that served as an antagonist to the cancer cell. It is recalled that on one occasion a not unnatural suggestion was made by a visiting physician who had witnessed the results of these experiments to the effect that possibly this curative principle might reside in the bodies of the leucocytes. The suggestion was recognized as having interest and plausibility, but the trend of thought at the moment was in the direction of chemical explanations of a less tangible kind, and no immediate attempt was made to verify or refute the leucocytic hypothesis. The matter came naturally to mind, however, when several years later, observation was made of the modification of blood count under influence of the protein treatment of human cancer subjects.

When the series of blood counts made in my experimental laboratory had reached the stage at which it became evident that there were highly interesting modifications of the leucocyte count (specifically characterized by an increase of mononuclear leucocytes, and in particular of the large mononuclears), it became a matter of interest to examine the literature of experimentation in quest of records of analogous experiences.

Then it became apparent that there is a peculiar paucity of observations on the differential count of the white corpuscles in an otherwise expansive literature; due, no doubt, to the fact that most workers have been concerned with the biochemical rather than the histological aspects of the investigation. It was, I think, the late Elbert Hubbard—voicing a familiar conclusion—who made the cogent observation that, in matters of science, we appear always to progress from the complex to the simple, and that the obvious is the last thing to be observed. Experiments in cancer inoculation with animals would seem to furnish another illustration of the truth of this observation, inasmuch as very tangible and obvious modifications of the blood count have for the most part been overlooked by workers who were concerning themselves with intricate problems of bodily metabolism involv-

ing chemical conditions susceptible of investigation only by the most delicate of biological methods.

Fortunately, however, there are a few workers who appear to have been impressed with the histological aspects of the problem, although even these have for the most part considered this aspect of the subject as having only subordinate interest.

Among the earliest and most important observations that associate the leucocytes with the process of immunization of animals against cancer inoculation are those of Bashford, Murray and Cramer, working under the auspices of the Imperial Cancer Research Fund, in England. In a report published in the Proceedings of the Royal Society of London for 1909, dealing with the general subject of resistant cancer inoculation, in mice, they make the following highly interesting observations:

"The phagocytosis of formed cellular elements plays an important role in inducing resistance; serum is impotent to induce resistance, blood corpuscles do so. The energetic phagocytosis which accompanies the spontaneous absorption of transplanted tumors, and which occurs in absorption after exposure to radium, speaks strongly for the conclusion that the processes are the same in kind when blood or tumor cells, being absorbed, produce resistence. But we are as yet unable to determine the extent to which agencies directed against the tumor cells themselves may assist in determining their early death in protected animals."

At an earlier stage of the series of investigation, the role of the leucocyte had been under consideration, as shown by a report made by Bashford, Murray, and Bowen, in the Proceedings of the Royal Society for 1906. In this report the authors say:

"Of course the cells presenting complete degeneration are no longer capable of giving rise to tumors. In fact they are rapidly taken up by the phagocytes in the days immediately preceding transplantation, and it might be concluded that growth was continued by cells which never tended to degenerate."

Incidentally it is of interest to note that in connection with this report the authors show a drawing of inoculated tumor tissues undergoing degeneration, in which portions of the mass that stain lightly are surrounded by cells with dark-staining nucleus and protoplasm of a type closely similar to cells that I have observed and studied in detail in a patient's blood taken from the immediate substance of a cancerous mass.

In continuance of the same line of observation, we find Da Fano in the Fifth Scientific Report of the Imperial Cancer Research Fund, issued in 1912, referring to the round cells that occur in the margin of a tumor that is retrograding, and along the strands of actively proliferating connective tissue. De Fano suggests that the development of tumor immunity in mice is coincident with the general reaction of the connective tissue throughout the organism. He observed that the polynuclear leu-

cocytes appear first at the place of the implanted tumor, and undergo degeneration, without showing phagocytic activity. The lymphocytes then appear in large numbers in the region of the inoculated tumor, gradually diminishing after immunity is established. According to his observation, inoculation of dead tumor cells was not followed by round cell infiltration nor by the development of tumor immunity. The observations were thought to establish a close relationship between the leucocytosis and the development of tumor immunity.

Dr. F. W. Baeslack, of Detroit, Mich., was led to take up a specific investigation of the modifications of the leucocytic blood count in mice suffering from transplanted tumors. The results of his researches were published in the *Zeitschrift für Immunitatsforschung* for 1913. He points out that the observation of the increase of leucocytes in cancer was made as long ago as 1843 by Andrae, and confirmed in detail by Lüdke in 1867. The latter observer concluded "that the increase in the number of leucocytes was a sign that the disease had become general and involved the whole body." Reference is made to other workers who have made observations on the leucocytes in cancer, but the list is a surprisingly short one considering the enormous bulk of cancer literature in general.

Dr. Baeslack's experiments had to do with several series of inoculated cancer mice. He states that his count of the blood cells included the large mononuclears and the eosinophiles, but his percentages and charts are given only for polynuclears and small lymphocytes. As to these he says:

"It is of interest to note that the small mononuclear lymphocytes decreased during the period of active tumor growth, while the polymorphonuclear leucocytes increased, and that shortly before the retrogression of the tumor became noticeable the relationship between these two classes of cells was entirely changed."

The charts presented give graphic illustration of the observation that when the polynuclear leucocytes went up and the small lymphocytes went down, the case was progressing badly. In one case at an early stage the polynuclears went up to 55 per cent. and the lymphocytes went down to 26 per cent. (It must be recalled that the polynuclears are relatively sparse—16.9 per cent., according to Price Jones—and lymphocytes relatively abundant—59.7 per cent.—in normal mouse-blood). But at a later stage, when the tumor was undergoing regression, the polynuclears went down to 16 per cent. (substantially normal), and the small lymphocytes advanced to 48 per cent. of the total leucocyte count, a number probably within the limits of normal variation.

It is unfortunate that details are not given as to the remaining types of leucocytes, but it is obvious that a simple computation shows that at the earlier stage of this experiment, when the tumor was seemingly overmastering the system, the large mononuclears and the eosinophiles together aggregated only 19 per cent. of the leucocyte count; whereas at a later stage, when the tumor was spontaneously regressing, the large monocytes and the eosinophiles together must have aggregated 36 per cent. of the total count, a number far in excess of the normal, which, according to Price Jones, is represented by 21.5 per cent. of large mononuclears and 0.14 of eosinophiles.

These observations of general lymphocytosis in cases of mouse tumors that are progressing to recovery have obvious interest as supplementing the observations of Da Fano to the effect that lymphocytes appeared in great numbers about inoculations of immunizing material during the evolution of resistance, and that in growing carcinomata the presence of the lymphocytes in great numbers was clearly associated with a local healing.

Further association between the corpuscles and the processes of immunization was suggested by the observations of Lambert and Haynes that rat sarcoma would grow in the plasma of immunized mice quite as vigorously as in that from normal or tumor-bearing animals,—an observation that obviously links with the observations on the curative properties of entire blood versus serum, as recorded at the beginning of this chapter.

From the present standpoint these observations as a whole have quite exceptional interest because they reveal modifications of the leucocyte count in mice in which tumors are undergoing regression that are singularly comparable to the records of the favorable case of human cancer under protein treatment observed by me and recorded in great detail before I had so much as heard of Dr. Baeslack's experiments. It will be recalled that charts were presented to illustrate graphically the fact that in cases that progressed most favorably under Proteal treatment the polynuclears and the small lymphocytes tended to approach the normal in numbers, whereas the large monocytes increased very markedly and held at high level.

It would appear that the same formula could be applied to Dr. Baeslack's convalescing mice; although the observer himself obviously failed to appreciate the significance of the large monocyte count, his attention being fixed solely on the polynuclears and small lymphocytes. Possibly he had overlooked, or was not aware of, the normal balance of leucocytes in mice (which, as just noted, is very different from that of the human subject), and hence did not realize that the fall of polynuclears to about 16 per cent. and the rise of lymphocytes to about 50 per cent., represented only

approximations to the normal; whereas the really significant feature of this count had to do with the large monocytes, which rose far above normal as the case progressed favorably (as we learn by subtracting the polymorphs and lymphocytes from the total count), yet which he did not think it worth while specifically to enumerate.

This correspondence between clinical experience with the human subject and laboratory observation of mice, as regards the modifications of leucocyte differential count when the system appears to be getting the better of a cancer invasion, is at least highly suggestive.

That Price Jones should have noted a rise of large monocytes in cancerous mice presumably not progressing favorably is obviously consistent with the thesis concerning the response to the presence of cancer cells exposited in detail in an earlier chapter of the present work; and it may be observed that the mice in question, as studied by Price Jones, showed increase in polynuclears also, precisely as did Baeslack's mice that were not recovering.

Of course it will not be overlooked that rise of polynuclears, taken by itself, is a phenomenon familiarly associated with bacterial infections, and that the latter may occur as a complication in many cases of malignant involvement. But it will be obvious that the modification of the differential count recorded in the protein-response tables is quite different from that induced by bacterial infection, inasmuch as a characteristic feature is the reduction rather than the increase of both relative and absolute polynuclear numbers.

Meantime it should be observed that students of the infections have tended to focus attention on the polynuclear "microphages" to the neglect of the mononuclear "macrophages." Even where the latter were counted, the possible significance of modifications of their numbers, is frequently overlooked or ignored. Thus in the very interesting and important studies of Gay and Claypole, as recorded in the *Archives of Internal Medicine* for November, 1914, in which the leucocytosis induced in normal and immunized rabbits by the injection of *Bacillus typhosus* is studied differentially, stress is laid entirely on the increase in polynuclears, although the facts recorded permit interesting inferences regarding the large mononuclears also, since the actual count of these cells twenty-four hours after inoculation showed an increase per cubic millimeter from 670 to 3,014—a four-and-a-half-fold advance. It is true that the advance of polynuclears was even more overwhelming (from 5,226 to 60,480); but on the other hand, the small lymphocytes advanced only from 7,370 to 11,340, an increase of but 54 per cent. suggesting by contrast that the four-and-a-half fold advance of the large lymphocytes is not to be

explained as a mere incidental result of general excitation of the blood-forming mechanism.

It is noteworthy in this connection that German clinicians (for example Von Domarus) cite an increase of large mononuclears as a typical feature of the secondary stage of a so-called "leucocyte-curve" of infections, such increase following the primary advance and recedence of the polynuclears, and preceding the advance of the small lymphocytes. Conceivably this macrocytosis is to provide for the hydrolysis of the protein products with which the blood has been flooded by the disintegration of the microphages (polynuclears) with their increment of partially digested bacteria. Such at any rate, might be a plausible explanation of the later aspects of the "leucocyte curve" if the proteomorphic thesis as to the proteolytic activities of large and small lymphocytes is accepted.

In general, it would appear that a relative monocytosis betokens a non-bacterial protein invasion as clearly as a neutrophile increase betokens a bacterial infection. Probably the diagnostic value of the monocytosis is not less than that of the polyneuclosis, although hitherto quite unrecognized.

Further pursuance of the subject here, however, would carry us too far afield from the present theme, which concerns malignant neoplasms rather than general infections. Let us again take up the analysis of the results of animal experimentation in the cancer field, with an eye to the correlation of these results with our own clinical and laboratory experience with cancer in the human subject.

Cart Before Horse

In considering various of the observations above cited, and numerous others in the literature of transplantable tumors in rats and mice, one is led to reflect on the power of preconception and the difference that may result from a changed point of view.

If a person who had seen automobiles moving about the streets, but who now for the first time saw a horse and carriage, were to describe what he had seen, he would doubtless tell of an automobile that pushed before it a strange animal. He might even note with amusement that the animal was obliged to move very rapidly to keep ahead of the vehicle that tends to overrun it. Probably he would be led to query why it would not be more convenient to tie the animal behind the vehicle and thus avoid the danger of injuring it.

Now such a description of the locomotion of the horse-drawn vehicle would, in my opinion, be strictly comparable to the descriptions that have appeared in the literature of cancer in connection with the question of the transplantation of tumors and the giving

of immunization. As a case in point, note the comment of a very industrious and laborious compiler, reviewing the literature of the subject, when referring to the experiments of De Fano, above noted, as follows:

"As lymphocytes appeared in great numbers about inoculations of immunizing material during the evolution of resistance, their relation to this condition could not be denied. . . . In growing carcinomata they were to be found only in places where local healing was in progress. A carcinoma cell seemed to exert some sort of specific influence on the lymphocyte, and the latter to spread the resistant state throughout the organism."

In the light of the interpretation of the action of the lymphocytes that furnishes the chief thesis of the present monograph, which will be elaborated presently, such a phrasing seems not less ridiculous than the suggestion that the horse is pushed before the carriage.

To say that lymphocytes "were found only in places where local healing was in progress" is a little as if one were to note the curious coincidence that, in a certain house, rats were to be found only in places where cheese was disappearing.

Scarcely less absurd seems the interpretation that has been put upon the widely heralded experiments of Ehrlich, as repeated by others, in what has come to be known as the zigzag transplantation of tumors. It will be recalled that in this experiment a tumor from a mouse is transplanted to the body of a rat, where it grows for a time, and then begins to undergo regression. Before it has entirely regressed, it is taken from the body of the rat and transferred to the original host, where it again takes on more or less energetic growth. It will be recalled that Ehrlich explained this with an elaborate theory of so-called atrepsia, according to which there are certain chemical constituents in the organism of the mouse that are essential to the growth of the mouse tumor; that a certain quantity of this material is transferred with the tumor to the body of the rat, and that when this transferred portion is exhausted, the growth can no longer continue in the body of the rat.

In the light of the present thesis, the explanation of zigzag transplantation would be simply that the transplanted tumor grew for a short time in the body of the rat because a certain time was required to muster the companies of corpuscles to combat the lawless cells. When the corpuscular defenders had been aggregated in sufficient numbers, the fight with the cancer cells would turn in favor of the host, and the cancer would begin to regress. Now, however, the remainder of the cancer cells are retransferred to the mouse, where, as a matter of course, they continue to grow because it had already been demonstrated that the body of that particular mouse was not competent to produce corpuscles and their

enzymes in sufficient quantity to combat the activities of the cancer cells.

A similar explanation, obviously, may be found for the observed fact that an animal may be rendered immune to inoculation experiments not merely by inoculation with the cancer tissue, but with tissues of various kinds, including heteromorphous ones. For example, Dr. Isaac Levin reported the immunization of rats by treatment with mouse tissue. (Proceedings of the Society for Experimental Biology and Medicine, 1910.) Other experimenters have produced immunization with the tissues of liver, spleen, and other organs. The evidence seems to justify the expectation that immunity may be developed by the introduction of various protein substance, whether derived from the tissues of animals of the same species, or of other species. In a word, it would appear that we have to do with a general protein reaction. Couple these observations with the observations of Bashford and his associates and of Baeslack, and we might fairly expect—were not our minds turned in the opposite direction—that an essential modification of the leucocyte count would be found in all of these cases; and we might justify the inference that such modification had an important relation to the process of immunization.

When, now, we turn to the human subject, and study the modifications of the blood count in cancer cases, and in particular cancer cases under protein treatment, as reported in the present monograph, it is obvious how all these observations of the animal experimenters harmonize with the results shown in our charts; and the conclusion seems inescapable that we have to do with a general principle of protein reaction, and with a response of the blood-forming organs one prominent feature of which is an increase in the phagocytic or enzymic activities of the corpuscles. This, after all, is only giving specific application, in terms of the protcomorphic theory, to the general conclusion stated by Levin in the paper above cited on the immunization of rats with mouse tissue, to the effect that: "The explanation must be sought in some protective substance within the host created under the influence of the implanted mouse tissue."

Phagocytic Activities

Before going on to a more detailed exposition of what I conceive to be the character and manner of action of this "protective substance," I would introduce a quotation from Starling's standard work on Physiology to remind the reader of the really extraordinary part that phagocytic activities play in physiological processes.

"We have seen," says Starling, "that the leucocytes from whatever animal they may be taken present two phenomena, viz., that of

amoeboid movement and that of ingesting foreign particles which may be presented to them. On account of this power of eating up foreign particles they are frequently spoken of as 'phagocytes,' in this respect resembling unicellular organisms and the undifferentiated cells of many kinds of tissue. All the phenomena connected with the process of *inflammation* in higher animals are directed to the assemblage of leucocytes at the spot which is the seat of injury or of infection, so that they may devour and remove either the injured tissue or the invading micro-organisms. This process plays therefore an important part in determining the immunity of any animal against infection; though in the higher animals it is assisted by a number of other mechanisms directed towards the same end, which we shall have to discuss in a subsequent chapter. The use of phagocytosis is not, however, confined to the protection of the organism against infection. Wherever any effete or dead tissue has to be cleared away, whether as the result of injury or in the course of metamorphosis of organs, the leucocytes play an important part. Thus in the great rearrangement of tissues which occurs in the larval state of insects, the removal of the muscle fibres which are no longer required is effected by the accumulation of phagocytes around them. The phagocytes may send processes into the muscle substance, which dissolve this tissue and then take it up. The absorption of the tail of the tadpole is effected in the same way by means of phagocytes. In mammals, including man, the moulding of the long bone which occurs in the process of growth is effected by continual and coincident processes of absorption and new formation of bone. The absorption is carried out by means of spinal phagocytes formed by the aggregation of a number of leucocytes, the well-known 'giant cells' or myeloplaxes which form so prominent a constituent of bone-marrow.

"The blood-corpuscles represent the *wandering* phagocytes of the body. There are *fixed* phagocytes of which the myeloplaxes just mentioned may be regarded as a type. Other members of this class are the endothelial cells (Kupfer's 'Sternzellen') which line the capillaries of the liver. If a suspension of carmine or of micro-organisms be injected into the blood stream these endothelial cells are found a little later to have taken up large numbers of the foreign bodies. Under normal circumstances these cells as well as some similar cells in the spleen take up effete red blood-corpuscles and destroy them. During the process of degeneration of a peripheral nerve brought about by its separation from the ganglion-cells of which its fibres are the processes, a marked proliferation of the nerve-nuclei takes place. These become surrounded with protoplasm and act the part of phagocytes, loading themselves with the fat globules set free by the degeneration of the myelin sheath. To the same class of fixed phagocytes may possibly be ascribed certain of the plasma-cells of the connective tissues.

"That the polymorphonuclear leucocytes are endowed with these phagocytic properties is universally acknowledged, but some

doubt still exists as to how far the other types of leucocytes which we have described can function as phagocytes. It is probable that the lymphocytes, and certainly the large mononuclear or hyaline corpuscles, are endowed with these properties. The granular corpuscles, namely, eosinophile and basophile, are thought by some to function as unicellular glands and to react to infection, not by englobing the micro-organisms, but by discharging substances stored up in their granules which have a poisonous effect on the micro-organisms, and so prepare them for subsequent ingestion by the polymorphonuclear leucocytes."

A very striking illustration of the phagocytic activities of leucocytes is given in certain abnormal conditions, notably in so-called phagocytic anaemia. This condition is characterized by active phagocytosis of blood cells by other blood cells of normal or abnormal type in the circulating blood. Ward says of this: "The resulting blood picture is very striking. In one case the phagocytosis was so pronounced that it was calculated that if all the cells were as actively phagocytic as one which was observed actually in perfect cells on the warm stage, the whole of the red cells of the body would have been destroyed in less than two hours. In this case the destruction produced a fatal anaemia. Other cases have followed transfusion or have been associated with some known haemolytic process such as cholaemia. Isolated phagocytic cells may be met with in malaria and leukaemia and no doubt in other diseases."

The active share that the large mononuclear leucocyte takes in this process is noted by Ward and graphically depicted in a drawing showing large mononuclear phagocytes, "Many of them containing several cells or portions of cells which have been caught." One of these mononuclear phagocytes appears to have engulfed no fewer than seven red corpuscles. Another has engulfed two large cells that have the appearance of polynuclears. The picture gives graphic support to the nomenclature of Metchnikoff, who designated the polynuclears as microphages and the large mononuclears as macrophages.

These activities of phagocytes may be recalled in connection with the observations already cited of similar functioning in the removal of the detritus of cancer cells, as noted by Bashford and his associates. It may be noted also that Walker, in dealing with the effect of certain serums on carcinoma in mice, observes that if pieces of tumor are placed in the serum of a rat which has been injected with extract of mouse testis, degeneration of the cancer cell takes place, the cells being invaded and replaced by leucocytes. It does not appear that this observation has been verified by other workers, but it has obvious interest in connection with the not dissimilar observations of the other workers already cited. In particular, note the observation of Bashford, Murray, and

Cramer as to the "energetic phagocytosis which accompanies spontaneous absorption of transplanted tumors, and which occurs in absorption after exposure to radium," and the observation of two of the same workers that cancer cells presenting complete degeneration "are rapidly taken up by phagocytes in the days immediately succeeding transplantation."

All in all, it would appear that there is abundant warrant for the assumption that the leucocytes have an important share in the attempt of the organism to combat the invasion of cancer cells. Probably the evidence justifies the belief that they have *the* important share, though the co-operation of the red corpuscles is so essential (according to the present thesis) that these agents can scarcely be said to be subordinate.

If this conclusion is justified, it would seem to follow as a matter of course that a medicinal agent to combat cancer should be sought along the lines of a stimulus to the blood-forming organs. It does not appear, however, that any one definitely formulated such an idea until an agent clinically observed to benefit the cancer subject was found to have acted through stimulation of the blood count—in particular increasing the numbers of red corpuscles and large mononuclears.

Types of Leucocytes

It will have been observed that throughout the foregoing discussion we have been concerned with concrete and tangible facts. Let us supplement these facts by recalling the series of tables in which it was demonstrated that the administration of vegetable proteins brings about, in the average cancer case, a conspicuous and progressive increase of the large mononuclear leucocytes, which were seen to advance from the normal maximum of four or five per cent. of the leucocyte count to 15 per cent., 18 per cent., 19 per cent., and 25 per cent., on the average, in successive groups of cases; reaching a much higher figure in individual cases.

With these series of facts for background, it will not be without interest to make inquiry as to the manner of action through which the increased armies of large monocytes exercise their antagonistic influence against cancer cells, and thus benefit the patient.

At the outset I would suggest the advisability of not drawing too sharp a line of distinction between the two types of mononuclear leucocytes, namely, the small lymphocytes and large monocytes. It must be recalled that there are still differences of opinion as to the origin of the large monocytes, some physiologists contending that they are merely overgrown lymphocytes. A more popular view, probably, is that they are of bone-marrow origin,

and the progenitors of the polymorphonuclear leucocytes. But whichever view is correct, it is scarcely in question that the mononuclear leucocytes represent a somewhat more primitive type of cell than the polynuclear. The polymorphs, eosinophiles, and basophiles are of granular structure, and it is held that the granules have a secretory function, generating enzymes that escape into the blood plasma. In keeping with this function, these cells have in general a relatively large cytoplasm, and their nuclear structure, although elaborated and differentiated in form, is relatively sparse, particularly in case of the fully developed polymorph.

Meantime, the typical lymphocyte is almost exclusively composed of nuclear structure; and the typical large monocyte has a relatively enormous nucleus and a relatively small amount of cytoplasm, as contrasted with the typical polynuclear cell. There is, however, a type of large mononuclear with nucleus less basic in stain than the typical large monocyte, and with full clear cytoplasm, which my personal studies lead me to associate with the cancer-cell destroying process, and which I am disposed to regard as of lymphoid origin—in effect an overgrown lymphocyte. Fuller discussion of the status of this and other types of large mononuclears is reserved for a later chapter.

In substantiation of the idea that the mononuclears are of a somewhat more primitive type than the polynuclears, we find the former relatively abundant in lower animals—for instance, the rabbit, with 60 per cent. of mononuclears; and the mouse, as already cited, with 80 per cent. or more of mononuclear cells, one-fourth of them large monocytes, and 17 per cent. of polynuclears, contrasted with the 70 per cent. of the latter in the human subject.

Witness also the fact that children show a relatively high percentage of mononuclears, at once evidencing the primitive character of these cells, and suggesting that they in some way functionate in connection with the control of rapidly growing tissues. In the first and second years of childhood, according to Von Domarus, the polynuclears represent only about 42 per cent. of the total leucocyte count, the small lymphocyte representing 47 per cent., the large monocyte (including transitionals) about 8 per cent., and the eosinophiles about 3 per cent. By the fifteenth year, the polynuclears have risen to more than 56 per cent., and the lymphocytes have dropped to about 28 per cent., but the large monocytes and transitionals are slightly more abundant than in infancy, representing about 9 per cent. of the leucocyte count, while the eosinophiles have risen to not far from 6 per cent. Between puberty and adult life there are further changes, resulting ultimately in giving the polynuclears a census not far from three-quarters of the total leucocyte count; the lymphocytes being

about one-third as numerous, and the large monocytes dropping to relative obscurity with a count of from two to four per cent.

It would appear, then, that the physiological conditions in the body of the normal mouse call for about five times as many large monocytes, proportionately, as are required in the body of an adult human being; and that the normal human being during childhood and adolescence requires about twice as many monocytes as are subsequently called for.

Note now the suggestive fact that, according to the observations of Cramer and Pringle, the tissue of a cancer (in mice) is of an embryonic type, as shown by the fact that its cells contain only about seventy per cent. of the nitrogen content of the average tissues of the host. Cramer had indicated the similarity between the growth of cancer and the growth of the foetus, and preliminary experiments by Dr. Lochstad had shown that a rapidly growing tissue (foetus) has a lower nitrogen value than the maternal organism. These experiments obviously confirm the old idea that cancer tissue is of somewhat embryonic character, and suggest the possibility that chemical or other agents might be found that would serve to decompound the cancer cells without injuring the normal surrounding tissue.

Natural Immunity and Artificial Immunization

Consider now for a moment the attitude—if the word be permitted—of the normal organism toward intruding cancer cells. Here the evidence must come largely from the field of animal experimentation, but it offers suggestive hints that may be applied, with due reserve, to the human subject.

It is familiarly known that the pioneer work of Hameu and Morau, expanded a little later by the work of Jensen and Leo Loeb, made possible a new era of investigation by showing that carcinomas and sarcomas of white mice and rats could be transplanted into other animals of the same species. It is equally well known that all experimenters are agreed that a certain number of individual animals show resistance to such transplantation, tumors embedded in their tissues regressing and disappearing "spontaneously" instead of continuing their lawless growth.

Thus it is shown, as Dr. Isaac Levin has phrased it, that "the growth of the implanted tumor depends upon the correlation between the virulence of the implanted cell and the resisting power of the organism of the host."

It was further shown that an artificial tumor used for inoculation appears to acquire increasing virulence as it is passed from one animal to another. But, on the other hand, it is possible to induce a condition in the body of an animal which at first is sus-

ceptible that will render it immune to further transplantation. This was done by Ehrlich and his associates by making an original inoculation with a tumor known to possess a low degree of virulence. Such a tumor being absorbed "spontaneously," it was observed that the animal in which such spontaneous absorption had occurred was now immune against inoculation with tumors of a more virulent type which would almost certainly have grown had not the animal been given added powers of resistance by the original inoculation.

What is of peculiar importance from the present standpoint is the fact that it was shown presently that inoculation with normal tissue, such as liver, spleen, and blood produced a degree of immunity comparable to that produced by the inoculation with a mild type of cancer cell. And most interesting of all is the observation of Dr. Levin and others that identical results as to induced immunity may be brought about by inoculation with so-called autolyzed tissue, that is to say, with tissue "of which the cells are killed in such a manner as to leave the endo-cellular enzyme-like substance uninjured and active."

I have quoted Dr. Levin's own phrase as to the use of autolyzed tissues, chiefly because it probably expresses the general attitude of mind of experimenters toward this particular aspect of the subject, in that it inferentially ascribes the immunizing influence of the autolyzed tissues to their "enzyme-like substance." It is hardly necessary to tell the reader of the present monograph, however, that in my own opinion the success of the experiment was due not to the presence of any specific enzymes, but to the fact that the tissue used—cancer tissue, liver tissue, spleen, blood, or what not—had the all-important advantage of being protein-bearing tissue.

This conclusion, to be sure, is inferential; but I think it will be admitted to find strong support in the fact that all manner of tissues, including even the tissues of an animal of another species (mouse tissues introduced into the rat, for example), can produce seemingly the same condition of immunity.

Note, now, the very significant fact that when a dog was cured of a transplanted tumor by the transfusion of blood of an immune animal in the later experiments made at the Loomis Laboratory, it was shown that decompounding and absorption of the tumor itself was an essential part of the immunizing process. This was proved by the fact that it was not found possible to render a dog immune to transplantation of a tumor by transfusing blood before such transplantation. It was only after the tumor had actually been transplanted and begun its growth, that the transfusion sufficed, through the process of destroying the tumor, to give the animal immunity against further inoculation.

Perhaps the most plausible explanation of this is found in the suggestion that the transfused blood contained corpusclar or enzymic substances that could begin the decompounding of the cancer cell, and that through such decompounding a stimulus was given to the blood-forming organs of the animal that led to an elaboration of the defensive mechanism that would not otherwise take place. The permanent modification of the conditions in the dog's system that made it resistant to future inoculation would thus be attributable to activities stimulated by the cancer proteins, acting virtually as autologous antigens.

In this view immunity thus induced is closely comparable to immunity induced by inoculation with autolyzed tissues.

No doubt it has occurred to a large number of workers, that, as Dr. Levin phrases it, "to induce an immunity to cancer growth may indicate the way to rational treatment of cancer, since such an immunity would prevent the occurrence of metastases, after the primary tumor is removed." But doubtless most such workers have felt, as Dr. Levin felt, that "it is self-evident that the results obtained cannot be transferred as yet to human pathology."

Had it occurred to any one, however, that the active agent involved was merely protein matter as such, and not enzymes specifically associated with or antagonistic to the cancer cell, there would have been no such embargo on transferring the research to human pathology.

But as the experimenters failed to gain this conception, the inviting possibilities were unrealized, and the clues to a solution of the problem were found in a quite different way. I have told the story in some detail elsewhere and it need not be repeated here.

The Value of Early Treatment

Among the most important of the observations of the animal experimenters, in their possible application to the human subjects, are those showing that (1) there is a marked distinction to be drawn between the original susceptibility of an animal to inoculation with cancer and the resistance to growth of the tumor in the same animal at a later period; and (2) the correlated fact that the same tumor appears to develop increasing virulence as it is brought through section and transplantation from the body of one animal to another.

As illustrating the first point, it is noted that a pregnant mouse is very insusceptible to inoculation with a tumor transplanted from another mouse, yet once the transplantation has been successfully effected, the tumor grows with extraordinary vigor.

A possible explanation of this would be that the pregnant animal has a system relatively well fortified against protein invasion,

due to the fact that there is a certain amount of proteid absorption from the placenta (the experiments of Abderhelden in this connection will be recalled), which led to a leucocytosis, and to the presence of an increased enzyme titer in the blood. In a word, the organism is well equipped to fight against the invasion of the protein cells represented by the cancer inoculation. If, however, in spite of this condition of preparedness, the cancer cells grow with such vigor that they prevail against the defending host, then it is not surprising that they take on very rapid development, because of the relatively large amount of nourishment that must be present in the blood and lymph channels of the pregnant animal to provide for the growth of the embryo.

It will be recalled that investigators have shown the chemical affinity between the rapidly growing tumor and the embryo—each of them containing a relatively low nitrogen content. In a sense, the foetus is in itself a foreign tumor, and one that takes on extraordinary rapidity of growth. Like the malignant tumor, the foetus has capacity for almost indefinite growth; and were it not possible presently to extrude the foetus it would become as great a menace to the life of the mother as the cancer itself. That thought need not be expanded here, however. From the present standpoint, the important thing is to recall that there is a distinction between the initial resistance to the early growth of a tumor and subsequent resistance to its later growth.

It is probable that this variation is not due solely to conditions in the system of the animal, but that it is also dependent in part on changed conditions of the tumor itself. This idea finds strong support in the observed increasing virulence of tumors as they pass from one organism to another. It seems plausible to suppose that this increasing virulence is at least in part a function of age; and to infer from this that cancer tissues in the same individual may gain increasing virulence as they grow older. The familiar fact that cancer cachexia appears only at the later stage of development of the malady in the human subject; coupled with the fact that metastatic secondary tumors very commonly grow with exceptional vigor, gives added support to this suggestion.

The obvious application of this line of reasoning is that there is an enormous premium on early treatment of cancer in the human subject—not merely treatment in the sense of cutting out the new growth as soon as it is discovered—though in many cases that may be desirable—but also in the sense of fortifying the defensive mechanism of the body by every available means. There is abundant clinical warrant for the belief that the protein treatment, for example, may accomplish results when administered to a patient having a new cancerous growth that could not be hoped for were the tumor a post-operative recurrence; the obvious ex-

planation being, in the light of what has just been said, that, on one hand, the new tumor is probably relatively non-virulent and, on the other hand, that the system of the patient has not had time to undergo so profound a condition of metabolic disturbance as accompanies the progress of the malady.

Results attained with relative ease at an early stage become almost impossible at a later stage, in which the cancer cells were additionally fortified and the bodily defenses progressively weakened. Stimulated by the presence of the abnormal cells, the blood-forming mechanism may ultimately reach a point of exhaustion which permits only a feeble response to new proteins. Myelocytes, leucoblasts and lymphoidocytes take the place of normal large monocytes; normal polymorphs are replaced by those of small, immature type; the lymphocytes are devoid of cytoplasm—a "starved" type; the red cells poikilocytic or nucleated.

This, assuredly, is not a hopeful picture. Yet even under such circumstances modifications in the blood in the direction of normality, and corresponding improvement in the general condition of the patient, together with modifications of the neoplasm, are sometimes effected by protein treatment within a relatively brief period, though not with spectacular suddenness. In one of my recent cases (No. 488), for example, a recurrent cancer of the breast rapidly developing about one year after removal, the blood count before treatment showed 33 per cent. of large mononuclear leucocytes, but very few of these were normal monocytes, the major part of them being of the leucoblast type. In the same count the polynuclears represented 53.3 per cent. and the small lymphocytes only 8 per cent., the eosinophiles 4.9 per cent.

After five days'treatment with rape protein, there was a very remarkable transformation. The leucoblasts had disappeared, possibly being transformed into polynuclears, since the latter now represented 69 per cent. of the white cell count. Large mononuclears were now only 4.6 per cent., but these were of the normal type, either of true monocytes with large nucleus and basic cytoplasm or of Ehrlich's transitionals. Meantime, there had been, seemingly, very active stimulation of the lymphatic system, since the small lymphocytes now numbered 23.5 per cent. Many of the lymphocytes were fairly large, and with a relatively large amount of cytoplasm. The eosinophiles were now only 1.5 per cent., but there were granular cells that stained dark, resembling the eosinophiles in structure rather than true basophiles, to the additional number of 4.3 per cent.

After another interval of five days, the leucocyte count had progressed still farther in the direction of normality, as regards the quality of the cells, the typical large monocytes now numbered 7.2 per cent.; the polynuclears 60.2 per cent.; lymphocytes

TABLE IX.—ORIGINAL CASES

A Group of Cases of Inoperable Cancer Still Under Observation and in Robust Condition After Prolonged Periods of Proteal Treatment (251 to 632 Days; Average, 424 Days)

Case No.	Name	Nature of Case	No. of Days	Hæmoglobin	Red Blood Corpuscles	White Blood Corpuscles	Polynuclears	Mononuclears		Eosinophiles	Basophiles
								Large	Small		
278	Mrs. B....	Rec. C. of Breast..	105	90	4,400,000		58.6	19	20.6	1.6	0
			180	100	5,408,000	7,500	72	17.3	8.6	2	0
			194	100	4,832,000	6,100	54.5	34	11.5	0	0
			475				57.4	13.7	26.8	1.7	0.7
16	Miss D....	Rec. C. of Breast..	93	90	4,464,000		59	17	24	0	0
			198	95	5,664,000	7,600	66.5	21.5	20	2	0
			215	100	5,252,000	7,500	61.5	13	24	1.5	0
			527		3,705,000	6,240	60	13.3	26.6	0.6	0
381	Mrs. H....	Melanoma.....	2	100	4,752,000	7,600	80.5	7.6	8.6	3.3	0
			16	100	4,448,000	8,000	78	10.5	7	4.5	0
			30	100	4,500,000	8,200	81	12.5	5	1	.5
			48	100	5,184,000	8,000	77.5	9.5	11	2	0
			324				67.5	21.5	8.5	.5	1.5
239	Mrs. M...	Car. of Breast....	142	90	5,376,000	7,200	64.3	16.3	15.6	3.6	0
			155	95	4,800,000	8,800	62.3	21.5	13	2	1
			172	100	5,096,000	8,000	60	23.5	13	2.5	1
			405				58	16	22	4	0
370	Mrs. R....	Ep. Car. of Hand..	5	95	4,896,000	10,200	72.6	14	10.6	2.6	0
			20	90	4,556,000	10,400	74	10	12	3.5	.5
			45	90	4,130,000	12,000	77.5	15	6.5	1	0
			311				58.4	30.3	5.8	5.4	.1
242	Mrs. S....	Ep. of Face.....	69	75	2,800,000		60	10.5	29	.5	0
			144	95	4,672,000	6,600	55.5	28	14.5	1	1
			155	100	4,672,000	7,200	50.5	31	15.5	3	0
			460				51	9	38.5	1.5	
332	Mrs. V. W.	Rec. C. of Breast..	50	85	5,008,000	8,880	64	16	24	0	0
			62	100	4,522,000	7,600	58.6	18.6	19.3	2.3	1
			76	100	4,448,000	7,400	55	17.5	15	2.5	0
			90	100	5,656,000	8,900	48.5	27	20.5	4	0
			394				39.3	17.6	41.6	1.3	0
			455	100	5,600,000	6,900	51	29.5	18.5	1	0
			505	100	5,610,000	6,600					
168	Miss W...	Rec. C. of Breast..	88	80	4,448,000		66.3	11.6	20	2	0
			112	95	4,240,000	8,000	67.3	21.6	10	.6	.3
			121	100	4,650,000	9,200	64.5	18	17	.5	0
			486				52.6	20.3	26	1.3	0
			632	100	5,177,000	9,100					
251	Mrs. W...	Rec. C. of Breast..	63	85	3,570,000		74	11	11	4	0
			138	85	5,280,000	9,400	68	16	9.5	6.5	0
			155	95	4,288,000	8,600	64.5	19.5	12	3	1
			467				63.6	9	20	6.6	
			509		6,044,000		60.3	8.3	22.6	8.3	
368	Mrs. C....	Rec. C. of Breast..	1	90	3,976,000	9,330	65.6	14.3	17.3	2.3	.3
			29	95	4,112,000	8,500	64.6	19	12.3	3.6	.3
			44	100	4,576,000	8,900	72	14.5	13	.5	0
			60	100	4,096,000	8,000	61.5	19.5	18	1	0
			312				55.3	16.6	28.3	2	0
543	Mr. F.....	C. of Stomach....	0	60	4,956,000	12,200	57	11	30	2	0
			7	75	4,364,000	8,500	59.5	19	21.5	0	0
			17	70	4,012,000	7,200					
			24	80	4,974,200	6,138					
			29				63.8	18.5	16.5	1	.5
			33	80	5,000,000	6,900	50	25.6	23.6	.6	
			41	85	4,988,000	8,800					
			228		4,644,000	8,200	70	12.5	12.5	4.6	
			243	85	4,848,000	9,600					
			251		4,320,000	6,400					

24.4 per cent.; eosinophiles 5.6 per cent.; basophiles 1.2 per cent. At this time study of the red cells showed a great abundance of normoblasts and free microblasts. Two weeks later, however, these had altogether disappeared (October 18th). The large monocytes, of normal type, now numbered 9.6 per cent.; the polymorphs stood practically unchanged at 59.6 per cent.; the lymphocytes had fallen to 19.6 per cent., and there were only 1 per cent. each of eosinophiles and basophiles. A month later (November 16th), the count showed continued progress, the polynuclears having fallen to 55.3 per cent., whereas large mononuclears had risen to 13.3 per cent., small lymphocytes to 27.3 per cent., and eosinophiles to 4 per cent.

The significant feature of this blood modification was the transformation from abnormal types to normal types of large mononuclears and the very notable increase of lymphocytes. The patient's general condition had meantime improved and there was a tendency to softening of the tumor mass in the breast, flattening of a large lymph node in the axilla, and marked regression of a subclavicular mass. It was not to be expected, however that very marked regression of the tumor would occur until the large monocyte count had been brought to a much higher state. The ultimate result must be left for future record. I mention the case here merely to illustrate a rather exceptional modification of the blood count, and to emphasize the point that in a case of such chronicity, in which the lymphatic system is seriously involved, with metastases, one must be content to go slowly, expecting no such spectacular metamorphosis as was recorded in the letter above quoted.

By way of contrast, note the progress of another recent case (No. 497) in which there was primary involvement of both breasts not far advanced. A surgeon had advised removal of both breasts, yet malignancy was considered doubtful by me until the blood count showed the following: polynuclears, 48.9 per cent.; large mononuclears (including myelocytes), 16.6 per cent.; small lymphocytes, 30.5 per cent.; eosinophiles, 4 per cent. The response to the proteal treatment was immediate; the patient reported a transformation in general health, and the blood count after three weeks of treatment (November 16, 1916) was: polynuclears, 43.6 per cent.; large monocytes, 21 per cent.; small lymphocytes, 33.6 per cent.; eosinophiles, 1.6 per cent.

The rapid response of this patient as contrasted with the preceding one may be ascribed, in all probability, to the early stage of development of the neoplastic growths.

With the emphasizing of this point, I may perhaps advantageously leave this aspect of the subject, reiterating the opinion that: here, as in so many other fields of pathology, there is a tremen-

dous premium on early treatment. Proteal remedies have indeed proved capable of giving solace in extraordinary measure to late stage inoperable cases of the most hopeless type; but the full measure of what may be expected of the new treatment can be gauged only when the Proteals have been administered to a large number of cases at an earlier stage of development.

SECTION XI

THE PREVENTION AND CURE OF CANCER

If the essential thesis of this paper as to the nature of cancer is accepted, and it is further accepted that the administration of vegetable proteins hypodermically tends to stimulate the enzymes capable of protein hydrolysis, certain practical suggestions as to the prevention of cancer; as to possible cure of the cancerous condition; and as to the obviation of its recurrence, follow almost as matters of course.

Since, however, things that seem obvious after one has devoted much thought to a subject are not always quite so plain to those who have thought along different lines, perhaps it may not be amiss to present here, partly by way of summary and recapitulation, a brief practical discussion of the prevention and the possible cure of the condition which I have characterized as hyperproteomorphism, with particular reference to that phase of the condition characterized by the presence of a malignant neoplasm or true cancer.

As to prevention, I shall speak only in the briefest terms. Whatever tends to maintain the general good health, keep the blood count normal, promote the normal digestion and nutrition, and keep the muscles (including those of the arterial walls) plastic, tends to ward off the cancerous condition.

No single expedient, in my judgment, is more important than habitual and vigorous exercise, particularly for persons in middle life and (modified in intensity) in old age. Keep the muscular system in really vigorous condition; avoid excess proteins in the food, in particular animal proteins; drink plenty of water; avoid all sources of general systemic irritation as well as local irritation, and there is at least a large measure of probability that the cancerous condition will never develop.

Once it has developed, however, and in particular when it has formed a local neoplasm of the type that we term epithelioma, carcinoma, or sarcoma, as the case may be, is there a possibility of a cure of the condition?

The answer must be, I think, that there is nothing inherent in the nature of the malady that makes it necessarily fatal (the results of animal experimentation appear to justify this verdict); but that, on the other hand, it is implied in the very nature of the condition that unless there can be a radical readjustment of the relations of the individual to his environment, the case is hopeless.

Merely to cut out the local neoplasm, and hope thus to cure the disease, is a childish procedure. The surgeon tells you that if you make the incision early enough and radical enough, all will be well. But, of course, you can never make the incision early enough nor radical enough. You could, to be sure, eradicate cancer of the uterus by universal hysterectomy in childhood, and annul cancer of the breast by universal amputation of infantile mammae. But such a procedure would have no conspicuous bearing on the cancerous condition, and would not in any way shield the organs that remained.

It is true that most surgeons claim a considerable proportion of "cures" following their operative procedures, particularly for cancer of the breast. But very few surgeons have cared to publish statistics as to the post-operative history of their cases, extending over a term of years. One surgeon of my personal acquaintance admits that when he attempted to follow up his cases he found that very few indeed were living three years after the operation, and only a single case after a lapse of five years.

Whether or not we accept that as a typical experience, it will be denied by no one that the usual and, so to say, expected history of a cancer case after operation is characterized by metastatic recurrence; that after a second and perhaps a third operation the case reaches an inoperable stage; and that inoperable cancer is universally regarded as among the most hopeless of conditions.

Speaking with the utmost conservatism, we can now say that experience justifies the statement that the Proteal treatment has come with at least a message of hope for these supposedly hopeless cases. As regards actual and permanent eradication of the diseased condition, doubtless this applies to only a small percentage of the cases hitherto treated by the new method. But that is merely equivalent to saying that the major part of the cases thus treated have been individuals whose systems were in so profound a state of disrepair that in the nature of the case they could not be mended.

Researches at the Mayo Clinic have made it clear to what an alarming extent changes that may be considered cancerous in character occur in other organs of the body than those directly effected either by the original neoplasm or by definite metastases.

These observations are obviously in keeping with the present thesis as to the general character of the cancerous condition. They accord also with a wide range of clinical experience. It is almost axiomatic to say that no two cases could be precisely alike as to the exact degree of involvement of the various organs and tissues of the body. Inherent susceptibilities of hereditary character, combined with accidental conditions of local irritation, would determine that in one case the liver, in another the pancreas, in a third the kidneys would have suffered most from the condition of nutritional maladjustments, in a series of cases in all of which the seat of the "primary cancer" might be, let us say, the breast, the stomach, or the uterus.

It is equally axiomatic to say that the precise location of metastatic masses and the precise relative degree of involvement of various organs affected without metastasis must be vastly important in its bearing on the prognosis of the case as regards imminence of the fatal issue.

Obviously, then, each case must be a law unto itself. If it is hazardous to generalize regarding conditions described merely as "cancer of the breast," "cancer of the uterus," etc., it is equally hazardous to attempt predictions as to the possible curability of any individual case thus described.

No one speaking with authority in connection with the Proteal treatment ever made such a prediction or held out the expectation of cure in any individual case. From the outset, in my publications and medical addresses on the subject, I have urged that a conservative attitude must be maintained as regards ultimate prognosis.

No one speaking with authority has suggested or expected that the proteins would perform the necromantic feat of restoring degenerated and decompounded cells of liver or spleen or kidneys or pancreas or intestinal glands. As well ask the surgeon to replace a lost arm or leg. Yet without such regeneration, in a large proportion of cases, it would be utterly futile to hope for the restoration of normal conditions of protein metabolism absolutely essential to health.

If, in such a case, the Proteal treatment favorably modified the blood count and made possible a temporary improvement in metabolism, thereby relieving the patient's distress, nullifying the obnoxious odors of a cancerous discharge, inducing a sense of well being, and prolonging life by a term of weeks or months while at the same time giving comfort—everything has been accomplished that could rationally be expected; everything, perhaps, that can never be hoped for in connection with the treatment of cases at so advanced a stage.

It should be added, however, that it is seldom possible to de-

termine with accuracy the precise stage of advancement of any given case, for the obvious reason that we cannot examine the structure of the various organs even if quantitative tests of their degree of involvement were available. A case that seems profoundly cachectic, and even almost moribund, may in reality have tissues less vitally involved than those of another case that has been tangibly affected for a much briefer period and in which the visible symptoms seem less alarming.

Hence it occasionally happens that a case in which the most optimistic estimate of a skilled observer would predict a very early demise responds to the treatment with unexpected vigor and rallies in a way which enthusiastic observers have not hesitated to speak of as "almost miraculous."

In a considerable number of instances, cases of this character have gone on, under the Proteal treatment, to a stage of improvement which may with validity be spoken of as clinical recovery. Whether or not the conditions of bodily metabolism have been permanently readjusted in such wise that the proliferation of misplaced cells will be prevented in future, must be left to the future to decide.

It may fairly be said, I think, that where a cancerous mass has thus retrogressed under the Proteal treatment there is greater inherent probability of non-recurrence than if it had disappeared under local treatment or through surgical interference; inasmuch as an improved condition of general bodily metabolism is implied in the results attained by the hypodermic method.

When treatment consisting exclusively of hypodermic injection into the tissue of the upper arm has resulted in the regression of a tumor mass in the pelvis, no argument is required to show that there has been profound modification of the condition of the body fluids. It is perhaps permissible to hope that this modification may have an element of permanency, or that it may be kept up by occasional administration of the hypodermic remedy, and that recurrence or metastasis of the localized cancerous mass will thus be prevented.

I repeat, that this is a matter for the future to decide. But I would suggest also that every practitioner who has successfully treated a case with Proteals should feel it incumbent upon him to urge his patient to have a blood count made at intervals of two or three months so long as he lives, and to submit himself to a new course of treatment should the blood show the slightest deviation from the standard. Doubtless it would be safer to take an occasional course of the treatment whatever the blood conditions. In any event, the treatment should not be discontinued for a good many weeks after the disappearance of the neoplasm.

That there should be most careful attention to the diet with

particular reference to the nitrogen balance, goes without saying. Careful attention should be given to all hygienic measures tending to promote general health. But in particular a régime of life should be adopted that includes daily systemic exercise of the most vigorous type consistent with the patient's condition of muscular tract. In my opinion, no single measure is more important than this; indeed, no other measure except that concerning the protein diet, approaches it in importance.

But these, after all, are matters regarding which the wise physician scarcely needs counseling. When it is clearly apprehended that the cancerous condition is due to a maladjustment of protein metabolism, it follows as a matter of course that all the measures commonly recognized as tending to reestablish the normal adjustment of such metabolism must be, in the first instance, preventative of cancer; in the second instance, invaluable as auxilliaries during the treatment of the malady, by whatever method; and, in the third place, indispensable as measures directed against recurrence of the malady.

But while all this, stated in general terms, seems fairly axiomatic, there goes with the suggestion the implication that no type of malady could give greater opportunity for the exercise of professional skill than the treatment of the cancerous condition. I have urged the futility of surgical treatment which is content merely to wield the knife and disregard all general measures. I would now urge that it would be only a degree less fatuous to suppose that adequate treatment of a cancer case by the protein method implies merely the random administration of a hypodermic. Yet a good many physicians who have used proteins have seemed to labor under this misapprehension. The correspondence is filled with letters from physicians of acknowledged standing who state that they have administered a dozen ampules, or two dozen ampules, of Proteals with remarkable results, and who now wish to ask if it is necessary to continue treatment.

A typical instance of this kind concerned a case of uterine cancer, originally operated upon and, after recurrence, pronounced inoperable at one of our most important metropolitan cancer hospitals, and subsequently radiumed without benefit and pronounced hopeless. Proteals had been turned to as a last resort, and eighteen doses had been administered in a term of about six weeks. And then the physician, without show of emotion, calmly inquires whether there is any necessity for further treatment,—a cure having seemingly been effected!

Needless to say the physician was urged to continue the treatment.

I cite this instance as illustrating how vague may be the conception of the true character of cancer in the minds of well-in-

formed physicians. Perhaps this is not surprising, considering that the available authorities differ so widely in their estimate of the nature of cancer. The fact that Metchnikoff advocated the theory of the germ origin of cancer no doubt has had great weight; and doubtless there are physicians who, in accepting this view, and having also in mind the conceivability of destroying disease germs at a single dose, or at the most with two or three doses, as was at first expected of Salvarsan, have thought that the Proteals might act in similar manner. Their expectations seem to be justified when the administration of two or three doses produces very striking modification in symptoms, including change in the character of the discharge, and a softening and tendency to regress in the neoplasm itself.

Even were cancer a germ disease (which I altogether disbelieve), and were it therefore possible to conceive a treatment that would eradicate the cause of the disease at a single coup, by the slaughter of bacteria, there would still remain the neoplasm itself, a proteid mass, to deal with. To expect that medication of any character would lead to the dissolution of the mass, when it is a large one, without profound systematic disturbance would be to misconceive the nature of the essential physiological conditions. It is neither to be expected nor desired that the protein matter making up the cancer should be hydrolyzed all at once, nor even with great rapidity. Were the enzymic attack on the cancer cells too active, the blood must become charged with the products of protein decompounding, and a tax would be put upon the cerebral tissues and the organs of elimination that they might not be able to withstand.

It follows that the carrying of a case of cancer under the proteal treatment to a favorable issue, even in the least complicated cases, is a matter demanding full measure of professional skill. I recall once hearing a somewhat distinguished artist say that anyone can *begin* the painting of a picture, but that it takes an artist to *finish it*. Similarly it may be said that any one can begin the proteal treatment of a case of cancer. Whoever can administer a hypodermic with ordinary aseptic precautions can secure definite results that are conspicuous and even notable in a great majority of cases. But to carry the case forward so that the effects are cumulative, and ultimately to secure the largest measure of benefit possible, requires skill of a high order.

If the best possible results are to be attained, it will be necessary not only to administer the treatment with constant observation of results as a guide to dosage and frequency of administration and the shifting from one proteal to another; but also to invoke, in many cases, the aid of supplementary measures.

First and foremost among these supplementary measures, is

the knife of the surgeon. It is true that the Proteals have hitherto been applied almost exclusively in inoperable cases. But in more than one instance it has happened that, under the influence of the remedy, a cancerous mass too widely extended for removal has regressed until the remaining mass is readily operable. In such a case, I would strongly urge that the co-operation of the surgeon should be sought, and the mass excised. By so doing, we relieve the system of the patient of the burden of absorption of a mass of protein tissue.

It will not usually be necessary, however, to make the surgical operation so radical, when Proteals are used, as it otherwise must be; inasmuch as the metastatic glands and the neighboring tissues —which at best the surgeon can remove but inadequately—are peculiarly subject to the proteolytic enzymes evoked by the administration of the hypodermic remedy.

It goes without saying, now that Proteal therapy supplies a means hitherto not available, to stimulate the production of the blood corpuscles and whip up their enzyme-forming capacities, that no surgeon of judgment will think of performing an operation for cancer without supplementing his surgical procedure with the use of Proteal remedies before and for some time after the operation.

It is essential, of course, to bear in mind the familiar phenomena of anaphylaxis, and to continue the administration of any given protein daily, or at intervals of two or three days at the most, until immunization is attained. It would obviously be inadvisable, after administering a given protein, to wait ten days or two weeks before administering a second dose of the same protein; since it is precisely under such conditions that the phenomena of anaphylaxis in its alarming form are likely to be developed. One protein, as is well known, does not fully immunize the system against another. Indeed, it is precisely this fact, as already pointed out, that furnished the basis for the theoretical administration of a series of proteins along the lines just suggested.

It has been pointed out that there is a wide range of variation among patients as regards their response to a given quantity of any foreign protein. The degree of susceptibility of individual patients must be determined by experiment.

It should be recalled, however, that in giving maximum doses one is introducing a relatively large quantity of foreign proteins and that these proteins must be dealt with by the bodily enzymes. So it may be accepted as a general principle of medication that the smallest dose that will produce a vigorous enzymic (corpuscular) response is the best dose.

There may come a time in the course of any individual case,

at which the enzymic response has reached the maximum. If, then, the administration of large doses of Proteals is continued at short intervals, the demands put upon the corpuscles in dealing with the proteins thus introduced may exhaust their resources, tending to induce a condition of pernicious anæmia.

The rational procedure in such a case is to discontinue for a time the administration of the protein to which the body has become "immunized"; either giving no treatment at all for a time (days or weeks, according to the progress of the case), or else substituting small doses of different proteins. In either case, the dose of the original protein should be small when its use is resumed. Patients who had discontinued the treatment for a term of weeks have repeatedly been observed, on resumption of the treatment, to react as vigorously to the small doses as if taking it for the first time.

From all this it will appear that no mere rule of thumb can be applied in determining the dosage, interval of administration, or length of treatment with protein antigens of any individual case of cancer. In general, it may be said that the dose to be aimed at is that which will carry the red blood count and the hæmoglobin test to the normal, and keep the large mononuclear leucocytes in adequate cohorts.

It should be recalled that no treatment can hope to produce better general systemic conditions than the individual patient experienced during his normal life; hence that every one who has suffered from cancer must always be more or less liable to recurrence,—unless, indeed, it should ultimately be shown that a measure of immunity results from regression of the neoplasm.

In other words, the cancer would not originally have developed had there not been certain inherent defects in the bodily mechanism of the individual. Often these defects are hereditary. Usually they are associated with the on-coming of old age, premature or otherwise. They mark a condition in which the capacity of the organism to deal with protein metabolism is waning. So this individual will probably always need the prop of an artificial stimulant to the cytogenic apparatus from time to time. Proteals supply such a prop. Their use will probably become routine practice not only in the post-operative treatment of cancer subjects, but in the after-year treatment of cases that have had the neoplasms removed by the action of Proteals themselves.

Obviously the same thing applies to cases treated successfully with X-ray and radium.

In a word, it may be expected that the province of Proteal therapy will be by no means confined to the *treatment* of cancer, but will have a place at least as important, and conceivably more important, in the prevention of recurrence after the local neoplasm

has been removed by any means whatsoever; and, ultimately also, no doubt, in prophylaxis applied to any person who through malnutrition, combined with some local source of irritation, has reason to fear the development of cancer.

Meantime this method gives to the individual cancer sufferer, whatever the stage of his malady, and to the physician who is called upon to treat him, the most enheartening message of hope that present-day therapeutics can offer.

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